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FILE 'REGISTRY' ENTERED AT 15:43:41 ON 13 JUL 2004

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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 11 JUL 2004 HIGHEST RN 708207-86-7

DICTIONARY FILE UPDATES: 11 JUL 2004 HIGHEST RN 708207-86-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> d ide l86 1-17; d ide l87 1-9

L86 ANSWER 1 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN

RN 156719-41-4 REGISTRY

CN L-Ornithine, N5-[imino(methylthio)methyl]- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN S-Methyl-L-thiocitrulline

CN S-Methylthiocitrulline

CN S-MTC

FS STEREOSEARCH

MF C7 H15 N3 O2 S

CI COM

SR CA

LC STN Files: BIOSIS, CA, CANCERLIT, CAPLUS, CEN, CHEMCATS, CSCHEM, MEDLINE, PROUSDDR, TOXCENTER, USPAT2, USPATFULL

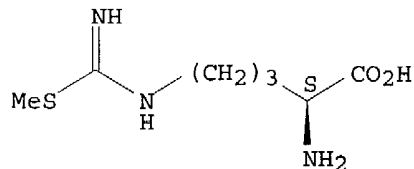
DT.CA Caplus document type: Journal; Patent

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

Absolute stereochemistry. Rotation (+).



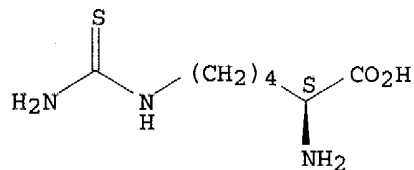
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

42 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
42 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 2 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN 156719-38-9 REGISTRY
CN L-Lysine, N6-(aminothioxomethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN L-Homothiocitrulline
FS STEREOSEARCH
MF C7 H15 N3 O2 S
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA Caplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: PREP (Preparation)

Absolute stereochemistry.

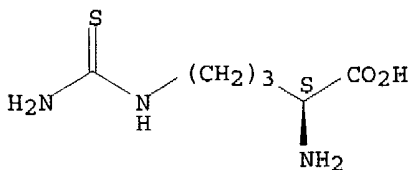


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 3 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN 156719-37-8 REGISTRY
CN L-Ornithine, N5-(aminothioxomethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN L-TC
CN L-Thiocitrulline
FS STEREOSEARCH
MF C6 H13 N3 O2 S
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CHEMCATS, CSCHEM, TOXCENTER, USPATFULL
DT.CA Caplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation)

Absolute stereochemistry.

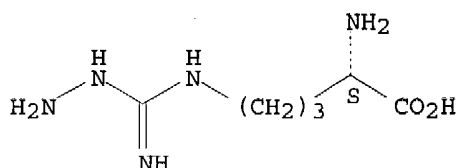


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

43 REFERENCES IN FILE CA (1907 TO DATE)
 3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 43 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 4 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 57444-72-1 REGISTRY
 CN L-Ornithine, N5-(hydrazinoiminomethyl)- (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN NG-Amino-L-arginine
 FS STEREOSEARCH
 MF C6 H15 N5 O2
 CI COM
 LC STN Files: CA, CANCERLIT, CAPLUS, MEDLINE, TOXCENTER, USPAT2, USPATFULL
 DT.CA Caplus document type: Journal; Patent
 RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
 RLD.P Roles for non-specific derivatives from patents: PREP (Preparation)
 RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

48 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 48 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 5 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 53774-63-3 REGISTRY
 CN L-Lysine, N6-(1-iminoethyl)- (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN .epsilon.-Acetimidylylsine
 CN L-NIL
 FS STEREOSEARCH
 MF C8 H17 N3 O2
 CI COM
 LC STN Files: ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, EMBASE, PROUSDDR, TOXCENTER, USPATFULL
 DT.CA Caplus document type: Journal; Patent
 RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES

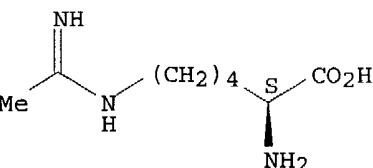
(Uses)

RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

85 REFERENCES IN FILE CA (1907 TO DATE)

2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

85 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 6 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN

RN 36889-13-1 REGISTRY

CN L-Ornithine, N5-(1-iminoethyl)- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN L-NIO

CN N.delta.-(Iminoethyl)-L-ornithine

CN N5-(1-Iminoethyl)-L-ornithine

FS STEREOSEARCH

MF C7 H15 N3 O2

CI COM

LC STN Files: BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CHEMCATS, CSCHEM, EMBASE, MEDLINE, TOXCENTER, USPAT2, USPATFULL

DT.CA CAplus document type: Dissertation; Journal; Patent

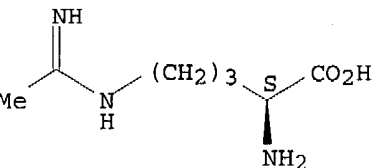
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation)

Absolute stereochemistry.

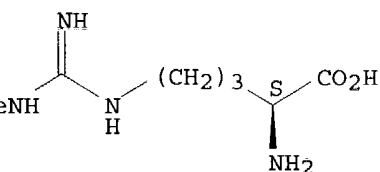


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

112 REFERENCES IN FILE CA (1907 TO DATE)
 2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 112 REFERENCES IN FILE CAPLUS (1907 TO DATE)

6 ANSWER 7 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
 17035-90-4 REGISTRY
 L-Ornithine, N5-[imino(methylamino)methyl]- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 Ornithine, N5-(methyamidino)-, L- (8CI)
 OTHER NAMES:
 .omega.-N-Methylarginine
 .omega.-N-Monomethylarginine
 L-Monomethylarginine
 L-NG-Methylarginine
 L-NMA
 L-NMMA
 Methylarginine
 N5-(Methyamidino)-L-ornithine
 NG-Methyl-L-arginine
 NG-methyl-L-arginine
 NG-Methylarginine
 NG-Monomethyl-L-arginine
 NG-Monomethylarginine
 Targinine
 STEREOSEARCH
 42342-68-7
 C7 H16 N4 O2
 COM
 STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS,
 BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CIN,
 CSCHEM, DDFU, DRUGU, EMBASE, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE,
 PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2,
 USPATFULL
 (*File contains numerically searchable property data)
 CA Caplus document type: Conference; Journal; Patent
 P Roles from patents: ANST (Analytical study); BIOL (Biological study);
 PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES
 (Uses)
 D.P Roles for non-specific derivatives from patents: BIOL (Biological
 study); USES (Uses)
 NP Roles from non-patents: ANST (Analytical study); BIOL (Biological
 study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP
 (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or
 reagent); USES (Uses)
 D.NP Roles for non-specific derivatives from non-patents: BIOL (Biological
 study); OCCU (Occurrence)

bsolute stereochemistry.

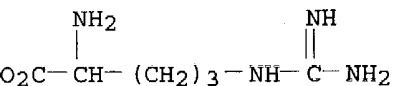


*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

879 REFERENCES IN FILE CA (1907 TO DATE)
 3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

879 REFERENCES IN FILE CAPLUS (1907 TO DATE)

86 ANSWER 8 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
 N 7200-25-1 REGISTRY
 N Arginine (9CI) (CA INDEX NAME)
 THER CA INDEX NAMES:
 N Arginine, DL- (8CI)
 N DL-Arginine
 THER NAMES:
 N (+-)-Arginine
 S 3D CONCORD
 F C6 H14 N4 O2
 I COM
 C STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
 CA, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DETHERM*,
 DIOGENES, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, MEDLINE,
 NAPRALERT, PIRA, PROMT, TOXCENTER, TULSA, USPAT2, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, NDSL**, TSCA**
 (**Enter CHEMLIST File for up-to-date regulatory information)
 T.CA Caplus document type: Conference; Journal; Patent
 L.P Roles from patents: ANST (Analytical study); BIOL (Biological study);
 FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process);
 RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
 LD.P Roles for non-specific derivatives from patents: BIOL (Biological
 study); USES (Uses)
 L.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological
 study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU
 (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT
 (Reactant or reagent); USES (Uses); NORL (No role in record)
 LD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical
 study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP
 (Properties); RACT (Reactant or reagent)



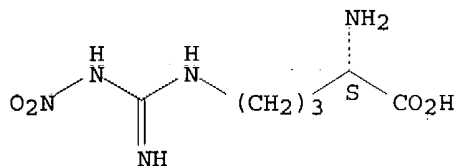
*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

319 REFERENCES IN FILE CA (1907 TO DATE)
 16 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 319 REFERENCES IN FILE CAPLUS (1907 TO DATE)

86 ANSWER 9 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
 N 2149-70-4 REGISTRY
 N L-Ornithine, N5-[imino(nitroamino)methyl]- (9CI) (CA INDEX NAME)
 THER CA INDEX NAMES:
 N Ornithine, N5-(nitroamidino)-, L- (8CI)
 THER NAMES:
 N (+)-NG-Nitroarginine
 N .omega.-Nitro-L-arginine
 N .omega.-Nitroarginine
 N L-Arginine, .omega.-nitro-
 N L-Arginine, NG-nitro-
 N L-NG-Nitroarginine
 N L-NNA
 N N.omega.-Nitro-L-arginine
 N N.omega.-Nitro-L-arginine

CN NG-Nitro-L-arginine
 CN NG-Nitroarginine
 CN Nitro-L-arginine
 CN Nitroarginine
 CN NOLA
 CN NSC 53662
 FS STEREOSEARCH
 DR 13855-78-2, 126265-23-4, 38733-00-5
 MF C6 H13 N5 O4
 CI COM
 LC STN Files: ADISNEWS, AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS,
 BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST,
 CIN, CSCHM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE,
 PROMT, PROUSDDR, RTECS*, SPECINFO, TOXCENTER, USPAT2, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, NDSL**, TSCA**
 (**Enter CHEMLIST File for up-to-date regulatory information)
 DT.CA CAPLUS document type: Conference; Dissertation; Journal; Patent
 RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC
 (Process); RACT (Reactant or reagent); USES (Uses)
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 RACT (Reactant or reagent); USES (Uses)
 RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological
 study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP
 (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or
 reagent); USES (Uses); NORL (No role in record)
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Absolute stereochemistry.

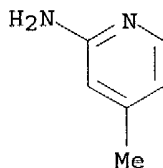


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

962 REFERENCES IN FILE CA (1907 TO DATE)
 21 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 963 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 10 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 695-34-1 REGISTRY
 CN 2-Pyridinamine, 4-methyl- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN 4-Picoline, 2-amino- (7CI, 8CI)
 OTHER NAMES:
 CN (4-Methylpyridin-2-yl)amine
 CN 2-Amino-.gamma.-picoline
 CN 2-Amino-4-methylpyridine
 CN 2-Amino-4-picoline
 CN 4-Methyl-2-aminopyridine
 CN 4-Methyl-2-pyridinamine
 CN 4-Methyl-2-pyridylamine
 CN Aminopicoline

CN Ascensil
 CN NSC 1490
 CN NSC 176165
 CN NSC 6972
 CN RA 1226
 CN VMI 20-4
 CN W 45
 CN W 45 Raschig
 FS 3D CONCORD
 DR 135995-51-6
 MF C6 H8 N2
 CI COM
 LC STN Files: ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS,
 CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU,
 EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, PS,
 RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, NDSL**, TSCA**
 (**Enter CHEMLIST File for up-to-date regulatory information)
 DT.CA Caplus document type: Conference; Journal; Patent; Report
 RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study);
 PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or
 reagent); USES (Uses); NORL (No role in record)
 RLD.P Roles for non-specific derivatives from patents: BIOL (Biological
 study); PREP (Preparation); PRP (Properties); RACT (Reactant or
 reagent); USES (Uses)
 RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological
 study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP
 (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or
 reagent); USES (Uses); NORL (No role in record)
 RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological
 study); FORM (Formation, nonpreparative); PREP (Preparation); PRP
 (Properties); RACT (Reactant or reagent); USES (Uses)

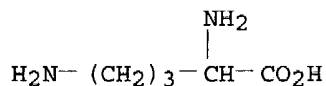


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

815 REFERENCES IN FILE CA (1907 TO DATE)
 15 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 817 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 16 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 11 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 616-07-9 REGISTRY
 CN **Ornithine (9CI)** (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN DL-Ornithine
 CN Ornithine, DL- (8CI)
 OTHER NAMES:
 CN (.+-.)-Ornithine
 CN (RS)-Ornithine
 FS 3D CONCORD
 MF C5 H12 N2 O2

CI COM
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CHEMLIST, CIN, CSCHM, DETHERM*, GMELIN*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, NAPRALERT, PROMT, TOXCENTER, TULSA, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: EINECS**
 (**Enter CHEMLIST File for up-to-date regulatory information)
 DT.CA Caplus document type: Conference; Dissertation; Journal; Patent
 RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
 RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
 RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
 RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

262 REFERENCES IN FILE CA (1907 TO DATE)
 23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 262 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 12 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 372-75-8 REGISTRY
 CN L-Ornithine, N5-(aminocarbonyl)- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Ornithine, N5-carbamoyl-, L- (8CI)
 OTHER NAMES:
 CN .alpha.-Amino-.delta.-ureidovaleic acid
 CN .delta.-Ureidonorvaline
 CN **Citrulline**
 CN L-Citrulline
 CN N.delta.-Carbamylornithine
 CN N5-Carbamoyl-L-ornithine
 CN NSC 27425
 FS STEREOSEARCH
 MF C6 H13 N3 O3
 CI COM
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHM, DDFU, DRUGU, EMBASE, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, PS, SPECINFO, TOXCENTER, USPAT2, USPATFULL, VETU
 (*File contains numerically searchable property data)
 Other Sources: EINECS**, NDSL**, TSCA**
 (**Enter CHEMLIST File for up-to-date regulatory information)
 DT.CA Caplus document type: Conference; Dissertation; Journal; Patent; Report
 RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation);

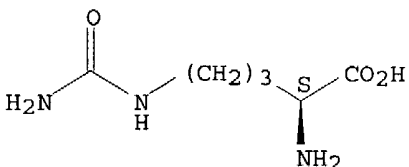
PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3565 REFERENCES IN FILE CA (1907 TO DATE)
 57 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 3571 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 69 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 13 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN

RN 79-17-4 REGISTRY

CN Hydrazinecarboximidamide (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Guanidine, amino- (8CI)

OTHER NAMES:

CN Aminate base

CN **Aminoguanidine**

CN Carbamimidic acid, hydrazide

CN Guanylhiazine

CN Monoaminoguanidine

CN Pimagedine

FS 3D CONCORD

DR 10331-66-5, 146396-78-3

MF C H6 N4

CI COM

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, DDFU, DRUGU, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
 (*File contains numerically searchable property data)

Other Sources: EINECS**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)

DT.CA Caplus document type: Conference; Dissertation; Journal; Patent; Report

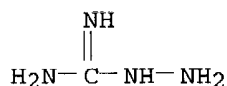
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.P Roles for non-specific derivatives from patents: ANST (Analytical

study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

1482 REFERENCES IN FILE CA (1907 TO DATE)
 66 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 1484 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 14 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 14 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 74-79-3 REGISTRY
 CN L-Arginine (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Arginine, L- (8CI)
 OTHER NAMES:
 CN (S)-2-Amino-5-[(aminoiminomethyl)amino]pentanoic acid
 CN **Arginine**
 CN L-(+)-Arginine
 CN L-.alpha.-Amino-.delta.-guanidinovaleric acid
 CN L-Arg
 CN L-Norvaline, 5-[(aminoiminomethyl)amino]-
 CN L-Ornithine, N5-(aminoiminomethyl)-
 CN NSC 206269
 CN Pentanoic acid, 2-amino-5-[(aminoiminomethyl)amino]-, (S)-
 FS STEREOSEARCH
 DR 667422-95-9, 7004-12-8, 142-49-4
 MF C6 H14 N4 O2
 CI COM
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PIRA, PROMT, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TULSA, USAN, USPAT2, USPATFULL, VETU
 (*File contains numerically searchable property data)
 Other Sources: DSL**, EINECS**, TSCA**, WHO
 (**Enter CHEMLIST File for up-to-date regulatory information)

DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent; Report

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

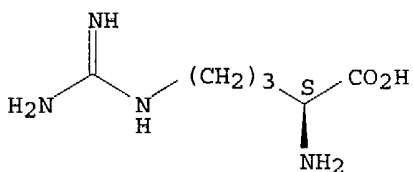
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU

(Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

38865 REFERENCES IN FILE CA (1907 TO DATE)
1084 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
38929 REFERENCES IN FILE CAPLUS (1907 TO DATE)
6 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 15 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN

RN 70-54-2 REGISTRY

CN **Lysine (9CI)** (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN DL-Lysine

CN Lysine, DL- (8CI)

OTHER NAMES:

CN (.+-.)-2,6-Diaminohexanoic acid

CN (.+-.)-Lysine

CN (RS)-Lysine

CN 2,6-Diaminohexanoic acid

CN DL-.alpha.,.epsilon.-Diaminocaproic acid

FS 3D CONCORD

MF C6 H14 N2 O2

CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DETHERM*, DIOGENES, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, MEDLINE, NAPRALERT, PIRA, PROMT, TOXCENTER, TULSA, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Other Sources: EINECS**

(**Enter CHEMLIST File for up-to-date regulatory information)

DT.CA CAPLUS document type: Conference; Dissertation; Journal; Patent; Report

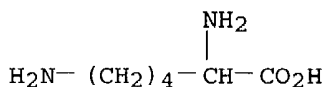
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological

study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)



****PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT****

637 REFERENCES IN FILE CA (1907 TO DATE)
26 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
637 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 16 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN

RN 70-26-8 REGISTRY

CN L-Ornithine (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Ornithine, L- (8CI)

OTHER NAMES:

CN (+)-S-Ornithine

CN (S)-.alpha.,.delta.-Diaminovaleric acid

CN (S)-2,5-Diaminopentanoic acid

CN (S)-Ornithine

CN L-(-)-Ornithine

CN L-Norvaline, 5-amino-

CN **Ornithine**

CN Pentanoic acid, 2,5-diamino-, (S)-

FS STEREOSEARCH

DR 7006-33-9, 410523-46-5

MF C5 H12 N2 O2

CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, SYNTHLINE, TOXCENTER, TULSA, USAN, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Other Sources: DSL**, EINECS**, TSCA**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)

DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent; Report

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

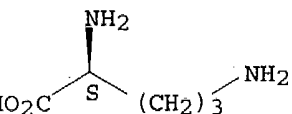
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses);

NORL (No role in record)

LD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

bsolute stereochemistry.



*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

7130 REFERENCES IN FILE CA (1907 TO DATE)
250 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
7141 REFERENCES IN FILE CAPLUS (1907 TO DATE)
4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

86 ANSWER 17 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN

56-87-1 REGISTRY

EN L-Lysine (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

EN Lysine, L- (8CI)

OTHER NAMES:

EN (+)-S-Lysine

EN (S)-.alpha.,.epsilon.-Diaminocaproic acid

EN (S)-2,6-Diaminohexanoic acid

EN (S)-Lysine

EN .alpha.-Lysine

EN 2,6-Diaminohexanoic acid

EN Aminutrin

EN Aminutrin, 6-amino-

EN h-Lys-oh

EN Hexanoic acid, 2,6-diamino-, (S)-

EN L-(+)-Lysine

EN L-2,6-Diaminocaproic acid

EN L-Lys

EN L-Norleucine, 6-amino-

EN **Lysine**

EN Lysine acid

CS STEREOSEARCH

DR 6899-06-5, 48050-57-3, 280114-50-3

MF C6 H14 N2 O2

CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TULSA, USAN, USPAT2, USPATFULL, VETU, VTB

(*File contains numerically searchable property data)

Other Sources: DSL**, EINECS**, TSCA**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)

OT.CA Cplus document type: Book; Conference; Dissertation; Journal; Patent; Preprint; Report

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC

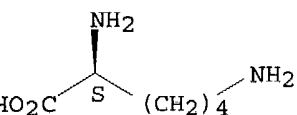
(Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

LD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles for non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

43181 REFERENCES IN FILE CA (1907 TO DATE)
1508 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
43241 REFERENCES IN FILE CAPLUS (1907 TO DATE)
7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

87 ANSWER 1 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN

RN 702694-01-7 REGISTRY

CN INDEX NAME NOT YET ASSIGNED

OTHER NAMES:

CN **N-Acetylcolchicinol dipotassium phosphate**

FS STEREOSEARCH

MF C20 H24 N O8 P . 2 K

SR CA

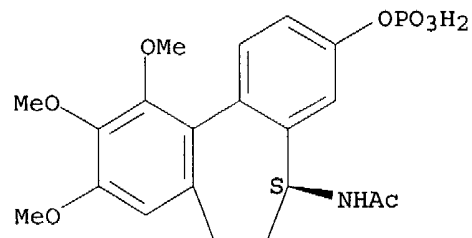
LC STN Files: CA, CAPLUS, TOXCENTER

DT.CA Caplus document type: Patent

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

CRN (219923-05-4)

Absolute stereochemistry.



●2 K

1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L87 ANSWER 2 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN

RN 702694-00-6 REGISTRY

CN INDEX NAME NOT YET ASSIGNED

OTHER NAMES:

CN **N-Acetylcolchicinol dilithium phosphate**

FS STEREOSEARCH

MF C20 H24 N O8 P . 2 Li

SR CA

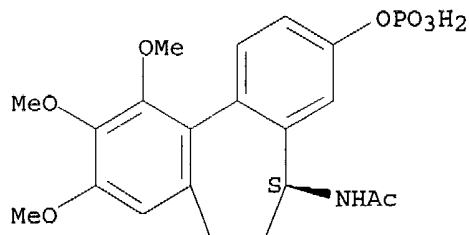
LC STN Files: CA, CAPLUS, TOXCENTER

DT.CA Caplus document type: Patent

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

CRN (219923-05-4)

Absolute stereochemistry.



●2 Li

1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L87 ANSWER 3 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN

RN 702693-99-0 REGISTRY

CN INDEX NAME NOT YET ASSIGNED

OTHER NAMES:

CN **N-Acetylcolchicinol disodium phosphate**

FS STEREOSEARCH

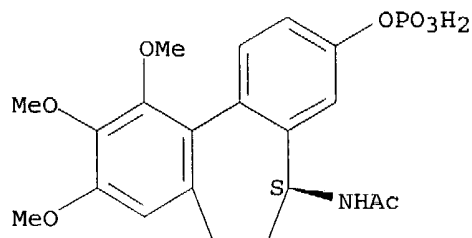
MF C20 H24 N O8 P . 2 Na

SR CA

LC STN Files: CA, CAPLUS, TOXCENTER

DT.CA CAplus document type: Patent
 RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
 CRN (219923-05-4)

Absolute stereochemistry.

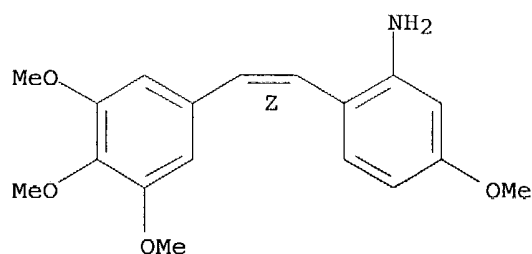


● 2 Na

1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L87 ANSWER 4 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 519060-26-5 REGISTRY
 CN **Benzenamine, 5-methoxy-2-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl] - (9CI)** (CA INDEX NAME)
 FS STEREOSEARCH
 MF C18 H21 N O4
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
 DT.CA CAplus document type: Patent
 RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Double bond geometry as shown.



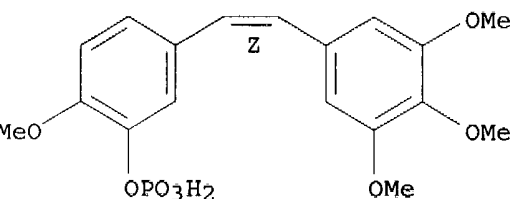
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L87 ANSWER 5 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 222030-63-9 REGISTRY
 CN **Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl] -, dihydrogen phosphate (9CI)** (CA INDEX NAME)
 OTHER NAMES:
 CN **Combretastatin A4 phosphate**

FS STEREOSEARCH
 MF C18 H21 O8 P
 CI COM
 SR CA
 LC STN Files: BIOSIS, CA, CAPLUS, CASREACT, EMBASE, IMSRESEARCH, PROUSDDR, TOXCENTER, USPAT2, USPATFULL
 DT.CA Caplus document type: Conference; Journal; Patent
 RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
 RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); USES (Uses)

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

39 REFERENCES IN FILE CA (1907 TO DATE)
 39 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L87 ANSWER 6 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 219923-05-4 REGISTRY
 CN Acetamide, N-[(5S)-6,7-dihydro-9,10,11-trimethoxy-3-(phosphonooxy)-5H-dibenzo[a,c]cyclohepten-5-yl]- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN **N-Acetylcolchicinol dihydrogenphosphate**

CN ZD 6126

FS STEREOSEARCH

MF C20 H24 N O8 P

CI COM

SR CA

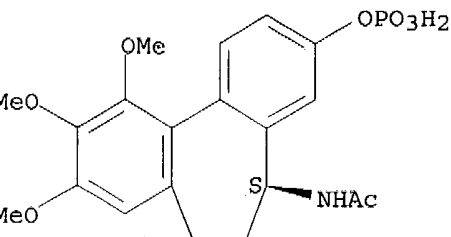
LC STN Files: BIOSIS, CA, CAPLUS, EMBASE, IMSRESEARCH, PROUSDDR, SYNTHLINE, TOXCENTER, USPATFULL

DT.CA Caplus document type: Journal; Patent

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

16 REFERENCES IN FILE CA (1907 TO DATE)
16 REFERENCES IN FILE CAPLUS (1907 TO DATE)

ANSWER 7 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN

168555-66-6 REGISTRY

Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, disodium salt (9CI) (CA INDEX NAME)

HER CA INDEX NAMES:

Phenol, 2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, disodium salt, (Z)-

HER NAMES:

CA 4P

Combretastatin A4 disodium phosphate

STEREOSEARCH

229027-07-0

C18 H21 O8 P . 2 Na

CA

STN Files: BIOSIS, CA, CAPLUS, CASREACT, EMBASE, IMSDRUGNEWS, IMSRESEARCH, PROUSDDR, TOXCENTER, USPAT2, USPATFULL

CA Caplus document type: Dissertation; Journal; Patent

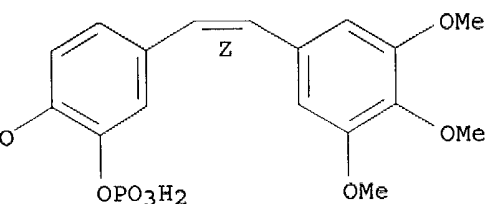
P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation)

N (222030-63-9)

Double bond geometry as shown.



● 2 Na

53 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

53 REFERENCES IN FILE CAPLUS (1907 TO DATE)

7 ANSWER 8 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN

117048-59-6 REGISTRY

Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)

HER CA INDEX NAMES:

Phenol, 2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, (Z)-

HER NAMES:

Combretastatin A4

CRC 87-09

NSC 817373

STEREOSEARCH

C18 H20 O5

COM

CA

STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, TOXCENTER, USPAT2, USPATFULL

(*File contains numerically searchable property data)

.CA Caplus document type: Conference; Dissertation; Journal; Patent

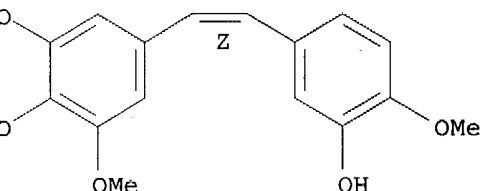
.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

.D.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

.D.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

175 REFERENCES IN FILE CA (1907 TO DATE)

16 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

177 REFERENCES IN FILE CAPLUS (1907 TO DATE)

7 ANSWER 9 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN

38838-26-5 REGISTRY

Acetamide, N-[(5S)-6,7-dihydro-3-hydroxy-9,10,11-trimethoxy-5H-dibenzo[a,c]cyclohepten-5-yl]- (9CI) (CA INDEX NAME)

HER CA INDEX NAMES:

5H-Dibenzo[a,c]cycloheptene, acetamide deriv.

Acetamide, N-(6,7-dihydro-3-hydroxy-9,10,11-trimethoxy-5H-dibenzo[a,c]cyclohepten-5-yl)-, (S)-

Colchinol, acetyl- (6CI)

Colchinol, N-acetyl- (7CI)

HER NAMES:

N-Acetylcolchicinol

N-Acetylcolchinol

NSC 51045

STEREOSEARCH

C20 H23 N O5

COM

STN Files: BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CHEMCATS, MEDLINE, PROUSDDR, RTECS*, TOXCENTER, USPATFULL

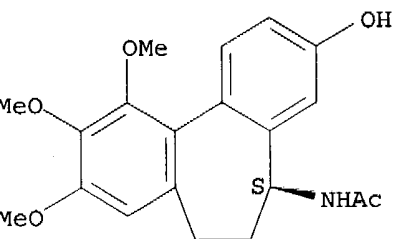
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.CA Caplus document type: Journal; Patent

.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation);
PROC (Process); RACT (Reactant or reagent); USES (Uses); NORL (No role
in record)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

39 REFERENCES IN FILE CA (1907 TO DATE)
39 REFERENCES IN FILE CAPLUS (1907 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> fil pascal jic biotechno esbio biotechds lifesci confsci dissabs toxcenter wpids
scisearch

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=> d que 185

L72 38460 SEA ((NITROGEN OR NITRIC) (W) OXIDE) (2A) (INHIB? OR ANTAGONI? OR
BLOCK?)
L73 16468 SEA AMINOPYRIDINE OR AMINO(1W) (PYRIDINE OR METHYLPYRIDINE)
L74 66 SEA IMINOETHYLORNITHINE OR IMINOETHYLLYSINE OR IMINOETHYLYSINE
L75 313189 SEA THIOCITRULLINE OR HOMOTHIOCITRULLINE OR ARGININE
OR ORNITHINE OR LYSINE OR CITRULLINE
L76 35184 SEA ALKYLTHIOUREA# OR THIOUREA# OR AMINOGUANIDINE OR
AMINO GUANIDINE
L77 1701 SEA TUBULIN BIND?
L78 902 SEA COMBRETASTATIN# (W) (A4 OR A 4) OR ACETYLCOLCHINOL
OR ACETYL COLCHINOL
L79 37277 SEA (NITROARGININE OR (METHYL OR NITRO OR AMINO)) (1W)
ARGININE OR METHYLARGININE OR AMINOARGININE
L81 57 SEA ((L72 OR L73 OR L74 OR L75 OR L76) OR L79) AND (L77 OR
L78)
L83 3501987 SEA INTERACT? OR SYNERG? OR POTENTIAT? OR CONCURRENT? OR
CODRUG# OR COADMIN? OR CO(W) (DRUG# OR ADMIN?)
L84 336957 SEA (THERAP? OR CHEMOTHERAP? OR DRUG#) (5A) COMB?
L85 29 SEA L81 AND ((L83 OR L84))

. fil capl; d que l28;d que l33
FILE 'CAPLUS' ENTERED AT 15:45:11 ON 13 JUL 2004
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FILE COVERS 1907 - 13 Jul 2004 VOL 141 ISS 3
FILE LAST UPDATED: 12 Jul 2004 (20040712/ED)

This file contains CAS Registry Numbers for easy and accurate
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OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

11 SEA FILE=REGISTRY ABB=ON (10102-43-9/BI OR 156719-37-8/BI OR
156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
57444-72-1/BI OR 695-34-1/BI)
1 SEA FILE=REGISTRY ABB=ON "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
10 SEA FILE=REGISTRY ABB=ON L4 NOT P/ELS
11 SEA FILE=REGISTRY ABB=ON NITRIC OXIDE/CN
12 9 SEA FILE=REGISTRY ABB=ON L10 NOT L11
13 1 SEA FILE=REGISTRY ABB=ON L-THIOCITRULLINE/CN
14 1 SEA FILE=REGISTRY ABB=ON L-HOMOTHIOCITRULLINE/CN
15 2 SEA FILE=REGISTRY ABB=ON ARGININE/CN
16 2 SEA FILE=REGISTRY ABB=ON ORNITHINE/CN
17 2 SEA FILE=REGISTRY ABB=ON LYSINE/CN
18 1 SEA FILE=REGISTRY ABB=ON CITRULLINE/CN
19 1 SEA FILE=REGISTRY ABB=ON AMINOGUANIDINE/CN
20 3 SEA FILE=REGISTRY ABB=ON COMBRETASTATIN A4?/CN
21 5 SEA FILE=REGISTRY ABB=ON N-ACETYLCHOLCHICINOL?/CN
22 1 SEA FILE=REGISTRY ABB=ON NITRIC OXIDE SYNTHASE/CN
23 10512 SEA FILE=CAPLUS ABB=ON (L11 OR L23 OR (NITROGEN/OBI OR
24 NITRIC/OBI) (W)OXIDE/OBI) (L) (INHIB?/OBI OR ANTAG?/OBI OR
BLOCK?/OBI)
25 72428 SEA FILE=CAPLUS ABB=ON (L12 OR L13 OR L14 OR L15 OR L16 OR
L17 OR L18 OR L19)
26 282 SEA FILE=CAPLUS ABB=ON L20 OR L21 OR L9
27 7 SEA FILE=CAPLUS ABB=ON (L26) AND (L24 OR L25)

11 SEA FILE=REGISTRY ABB=ON (10102-43-9/BI OR 156719-37-8/BI OR
156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
57444-72-1/BI OR 695-34-1/BI)
1 SEA FILE=REGISTRY ABB=ON "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN

L10 10 SEA FILE=REGISTRY ABB=ON L4 NOT P/ELS
 L11 1 SEA FILE=REGISTRY ABB=ON NITRIC OXIDE/CN
 L12 9 SEA FILE=REGISTRY ABB=ON L10 NOT L11
 L13 1 SEA FILE=REGISTRY ABB=ON L-THIOCITRULLINE/CN
 L14 1 SEA FILE=REGISTRY ABB=ON L-HOMOTHIOCITRULLINE/CN
 L15 2 SEA FILE=REGISTRY ABB=ON ARGININE/CN
 L16 2 SEA FILE=REGISTRY ABB=ON ORNITHINE/CN
 L17 2 SEA FILE=REGISTRY ABB=ON LYSINE/CN
 L18 1 SEA FILE=REGISTRY ABB=ON CITRULLINE/CN
 L19 1 SEA FILE=REGISTRY ABB=ON AMINOGUANIDINE/CN
 L20 3 SEA FILE=REGISTRY ABB=ON COMBRETASTATIN A4?/CN
 L21 5 SEA FILE=REGISTRY ABB=ON N-ACETYLCHOLCHICINOL?/CN
 L22 1060 SEA FILE=CAPLUS ABB=ON TUBULIN#/OBI(3A)BIND?/OBI
 L23 1 SEA FILE=REGISTRY ABB=ON NITRIC OXIDE SYNTHASE/CN
 L24 10512 SEA FILE=CAPLUS ABB=ON (L11 OR L23 OR (NITROGEN/OBI OR
 NITRIC/OBI) (W)OXIDE/OBI) (L) (INHIB?/OBI OR ANTAG?/OBI OR
 BLOCK?/OBI)
 L25 72428 SEA FILE=CAPLUS ABB=ON (L12 OR L13 OR L14 OR L15 OR L16 OR
 L17 OR L18 OR L19)
 L26 282 SEA FILE=CAPLUS ABB=ON L20 OR L21 OR L9
 L32 33604 SEA FILE=CAPLUS ABB=ON DRUG INTERACTIONS+OLD,NT/CT OR DRUG
 DELIVERY SYSTEMS+OLD/CT(L)COMB?/OBI
 L33 2 SEA FILE=CAPLUS ABB=ON (L22 OR L26) AND (L24 OR L25) AND L32

=> s l28 or l33

L88 7 L28 OR L33

=> fil uspatf; d que l38; fil medl; d que l49

FILE 'USPATFULL' ENTERED AT 15:45:27 ON 13 JUL 2004

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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 13 Jul 2004 (20040713/PD)

FILE LAST UPDATED: 13 Jul 2004 (20040713/ED)

HIGHEST GRANTED PATENT NUMBER: US2004126357

HIGHEST APPLICATION PUBLICATION NUMBER: US2004133957

CA INDEXING IS CURRENT THROUGH 13 Jul 2004 (20040713/UPCA)

ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 13 Jul 2004 (20040713/PD)

REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2004

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>>> USPAT2 is now available. USPATFULL contains full text of the <<<
 >>> original, i.e., the earliest published granted patents or <<<
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 >>> publications, starting in 2001, for the inventions covered in <<<
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 >>> published document but also a list of any subsequent <<<
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L4      11 SEA FILE=REGISTRY ABB=ON (10102-43-9/BI OR 156719-37-8/BI OR
        156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
        BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
        57444-72-1/BI OR 695-34-1/BI)
L9      1 SEA FILE=REGISTRY ABB=ON "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
        4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
L10     10 SEA FILE=REGISTRY ABB=ON L4 NOT P/ELS
L11     1 SEA FILE=REGISTRY ABB=ON NITRIC OXIDE/CN
L12     9 SEA FILE=REGISTRY ABB=ON L10 NOT L11
L13     1 SEA FILE=REGISTRY ABB=ON L-THIOCITRULLINE/CN
L14     1 SEA FILE=REGISTRY ABB=ON L-HOMOTHIOCITRULLINE/CN
L15     2 SEA FILE=REGISTRY ABB=ON ARGININE/CN
L16     2 SEA FILE=REGISTRY ABB=ON ORNITHINE/CN
L17     2 SEA FILE=REGISTRY ABB=ON LYSINE/CN
L18     1 SEA FILE=REGISTRY ABB=ON CITRULLINE/CN
L19     1 SEA FILE=REGISTRY ABB=ON AMINOGUANIDINE/CN
L20     3 SEA FILE=REGISTRY ABB=ON COMBRETASTATIN A4?/CN
L21     5 SEA FILE=REGISTRY ABB=ON N-ACETYLCHOLCHICINOL?/CN
L23     1 SEA FILE=REGISTRY ABB=ON NITRIC OXIDE SYNTHASE/CN
L34     713 SEA FILE=USPATFULL ABB=ON (L11 OR L23 OR ((NITRIC OR NITROGEN)
        (W)OXIDE)/IT) (L) (INHIB? OR ANTAG? OR BLOCK?)/IT
L35     3964 SEA FILE=USPATFULL ABB=ON (L12 OR L13 OR L14 OR L15 OR L16 OR
        L17 OR L18 OR L19)
L36     51 SEA FILE=USPATFULL ABB=ON (TUBULIN#(3A)BIND?)/IT, TI, AB, CLM
L37     62 SEA FILE=USPATFULL ABB=ON L9 OR (L20 OR L21)
L38     1 SEA FILE=USPATFULL ABB=ON (L34 OR L35) AND (L36 OR L37)

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FILE 'MEDLINE' ENTERED AT 15:45:27 ON 13 JUL 2004

FILE LAST UPDATED: 10 JUL 2004 (20040710/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLD MEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

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L4      11 SEA FILE=REGISTRY ABB=ON (10102-43-9/BI OR 156719-37-8/BI OR
        156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
        BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
        57444-72-1/BI OR 695-34-1/BI)
L9      1 SEA FILE=REGISTRY ABB=ON "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
        4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
L10     10 SEA FILE=REGISTRY ABB=ON L4 NOT P/ELS
L11     1 SEA FILE=REGISTRY ABB=ON NITRIC OXIDE/CN
L12     9 SEA FILE=REGISTRY ABB=ON L10 NOT L11
L13     1 SEA FILE=REGISTRY ABB=ON L-THIOCITRULLINE/CN
L14     1 SEA FILE=REGISTRY ABB=ON L-HOMOTHIOCITRULLINE/CN
L15     2 SEA FILE=REGISTRY ABB=ON ARGININE/CN
L16     2 SEA FILE=REGISTRY ABB=ON ORNITHINE/CN
L17     2 SEA FILE=REGISTRY ABB=ON LYSINE/CN

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L18      1 SEA FILE=REGISTRY ABB=ON CITRULLINE/CN
L19      1 SEA FILE=REGISTRY ABB=ON AMINO GUANIDINE/CN
L20      3 SEA FILE=REGISTRY ABB=ON COMBRETASTATIN A4?/CN
L21      5 SEA FILE=REGISTRY ABB=ON N-ACETYL COLCHICINOL?/CN
L39      7734 SEA FILE=MEDLINE ABB=ON NITRIC-OXIDE SYNTHASE/CT(L)AI/CT
L40      2576 SEA FILE=MEDLINE ABB=ON NITRIC OXIDE/CT(L)AI/CT
L41      50385 SEA FILE=MEDLINE ABB=ON (L12 OR L13 OR L14 OR L15 OR L16 OR
L17 OR L18 OR L19)
L43      1371 SEA FILE=MEDLINE ABB=ON TUBULIN#(3A)BIND?
L44      108 SEA FILE=MEDLINE ABB=ON L9 OR (L20 OR L21)
L45      173 SEA FILE=MEDLINE ABB=ON COMBRETASTATIN#(W)(A 4 OR A4) OR
ACETYL COLCHINOL#
L47      2441 SEA FILE=MEDLINE ABB=ON ANGIOGENESIS INHIBITORS/CT
L48      203563 SEA FILE=MEDLINE ABB=ON DRUG INTERACTIONS+NT/CT OR DRUG
COMBINATIONS/CT OR DRUG THERAPY, COMBINATION/CT
L49      3 SEA FILE=MEDLINE ABB=ON (L39 OR L40 OR L41) AND (L43 OR L44
OR L45) AND (L47 OR L48)

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=> fil embase; d que l57; fil biosis; d que l64; fil drugu; d que l71
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156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
57444-72-1/BI OR 695-34-1/BI)
L9      1 SEA FILE=REGISTRY ABB=ON "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
L10     10 SEA FILE=REGISTRY ABB=ON L4 NOT P/ELS
L11     1 SEA FILE=REGISTRY ABB=ON NITRIC OXIDE/CN
L12     9 SEA FILE=REGISTRY ABB=ON L10 NOT L11
L13     1 SEA FILE=REGISTRY ABB=ON L-THIOCITRULLINE/CN
L14     1 SEA FILE=REGISTRY ABB=ON L-HOMOTHIOCITRULLINE/CN
L15     2 SEA FILE=REGISTRY ABB=ON ARGININE/CN
L16     2 SEA FILE=REGISTRY ABB=ON ORNITHINE/CN
L17     2 SEA FILE=REGISTRY ABB=ON LYSINE/CN
L18     1 SEA FILE=REGISTRY ABB=ON CITRULLINE/CN
L19     1 SEA FILE=REGISTRY ABB=ON AMINO GUANIDINE/CN
L20     3 SEA FILE=REGISTRY ABB=ON COMBRETASTATIN A4?/CN
L21     5 SEA FILE=REGISTRY ABB=ON N-ACETYL COLCHICINOL?/CN
L50     40590 SEA FILE=EMBASE ABB=ON (L12 OR L13 OR L14 OR L15 OR L16 OR
L17 OR L18 OR L19)
L51     6565 SEA FILE=EMBASE ABB=ON NITRIC OXIDE SYNTHASE INHIBITOR/CT
L52     43922 SEA FILE=EMBASE ABB=ON NITRIC OXIDE/CT
L53     194 SEA FILE=EMBASE ABB=ON L9 OR (L20 OR L21)
L54     19 SEA FILE=EMBASE ABB=ON N ACETYL COLCHINOL PHOSPHATE/CT OR N
ACETYL COLCHINOL/CT
L55     176 SEA FILE=EMBASE ABB=ON COMBRETASTATIN A4/CT
L56     2 SEA FILE=EMBASE ABB=ON TUBULIN BINDING AGENT/CT
L57     8 SEA FILE=EMBASE ABB=ON (L50 OR L51 OR L52) AND (L53 OR L54 OR
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FILE RELOADED: 19 October 2003.

L4 11 SEA FILE=REGISTRY ABB=ON (10102-43-9/BI OR 156719-37-8/BI OR
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BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
57444-72-1/BI OR 695-34-1/BI)
L9 1 SEA FILE=REGISTRY ABB=ON "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
L10 10 SEA FILE=REGISTRY ABB=ON L4 NOT P/ELS
L11 1 SEA FILE=REGISTRY ABB=ON NITRIC OXIDE/CN
L12 9 SEA FILE=REGISTRY ABB=ON L10 NOT L11
L13 1 SEA FILE=REGISTRY ABB=ON L-THIOCITRULLINE/CN
L14 1 SEA FILE=REGISTRY ABB=ON L-HOMOTHIOCITRULLINE/CN
L15 2 SEA FILE=REGISTRY ABB=ON ARGININE/CN
L16 2 SEA FILE=REGISTRY ABB=ON ORNITHINE/CN
L17 2 SEA FILE=REGISTRY ABB=ON LYSINE/CN
L18 1 SEA FILE=REGISTRY ABB=ON CITRULLINE/CN
L19 1 SEA FILE=REGISTRY ABB=ON AMINOGUANIDINE/CN
L20 3 SEA FILE=REGISTRY ABB=ON COMBRETASTATIN A4?/CN
L21 5 SEA FILE=REGISTRY ABB=ON N-ACETYL COLCHICINOL?/CN
L58 43595 SEA FILE=BIOSIS ABB=ON (L12 OR L13 OR L14 OR L15 OR L16 OR
L17 OR L18 OR L19)
L59 15292 SEA FILE=BIOSIS ABB=ON ((NITROGEN OR NITRIC) (W) OXIDE) (2A) (INHI
B? OR ANTAGONI? OR BLOCK?)
L60 134 SEA FILE=BIOSIS ABB=ON L9 OR L21 OR L20
L61 235 SEA FILE=BIOSIS ABB=ON COMBRETASTATIN#(W) (A4 OR A 4) OR
ACETYL COLCHINOL OR ACETYL COLCHINOL
L64 6 SEA FILE=BIOSIS ABB=ON (L58 OR L59) AND (L60 OR L61)

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>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<

>>> THESAURUS AVAILABLE IN /CT <<<

>>> A RECENT REVIEW OF PSYCHIATRIC DISEASE KEYWORDS USED
IN DERWENT DRUG FILE HAS PROMPTED A REVISION BASED
ON STANDARD TERMS USED IN DSM-IV (DIAGNOSTIC AND
STATISTICAL MANUAL OF MENTAL DISORDERS - FOURTH
EDITION).

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http://thomsonderwent.com/derwenthome/support/userguides/lit_guide

L4 11 SEA FILE=REGISTRY ABB=ON (10102-43-9/BI OR 156719-37-8/BI OR

156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
57444-72-1/BI OR 695-34-1/BI)
1 SEA FILE=REGISTRY ABB=ON "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
10 SEA FILE=REGISTRY ABB=ON L4 NOT P/ELS
1 SEA FILE=REGISTRY ABB=ON NITRIC OXIDE/CN
9 SEA FILE=REGISTRY ABB=ON L10 NOT L11
1 SEA FILE=REGISTRY ABB=ON L-THIOCITRULLINE/CN
1 SEA FILE=REGISTRY ABB=ON L-HOMOTHIOCITRULLINE/CN
2 SEA FILE=REGISTRY ABB=ON ARGININE/CN
2 SEA FILE=REGISTRY ABB=ON ORNITHINE/CN
2 SEA FILE=REGISTRY ABB=ON LYSINE/CN
1 SEA FILE=REGISTRY ABB=ON CITRULLINE/CN
1 SEA FILE=REGISTRY ABB=ON AMINOGUANIDINE/CN
3 SEA FILE=REGISTRY ABB=ON COMBRETASTATIN A4?/CN
5 SEA FILE=REGISTRY ABB=ON N-ACETYLCOLCHICINOL?/CN
1203 SEA FILE=DRUGU ABB=ON (L12 OR L13 OR L14 OR L15 OR L16 OR L17
OR L18 OR L19)
3713 SEA FILE=DRUGU ABB=ON ((NITROGEN OR NITRIC) (W)OXIDE) (2A) (INHIB
? OR ANTAGONI? OR BLOCK?)
102 SEA FILE=DRUGU ABB=ON L9 OR (L20 OR L21)
243 SEA FILE=DRUGU ABB=ON COMBRETASTATIN#(W) (A4 OR A 4) OR
ACETYLCOLCHINOL OR ACETYL COLCHINOL
204 SEA FILE=DRUGU ABB=ON TUBULIN# BINDING
4 SEA FILE=DRUGU ABB=ON (L66 OR L67) AND (L68 OR L69 OR L70)

dup rem 149,171,188,164,157,185,138

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ROCESSING COMPLETED FOR L49
ROCESSING COMPLETED FOR L71
ROCESSING COMPLETED FOR L88
ROCESSING COMPLETED FOR L64
ROCESSING COMPLETED FOR L57
ROCESSING COMPLETED FOR L85
ROCESSING COMPLETED FOR L38

39 27 DUP REM L49 L71 L88 L64 L57 L85 L38 (31 DUPLICATES REMOVED)

ANSWERS '1-3' FROM FILE MEDLINE
ANSWERS '4-7' FROM FILE DRUGU
ANSWERS '8-11' FROM FILE CAPLUS
ANSWERS '12-13' FROM FILE BIOSIS
ANSWERS '14-19' FROM FILE EMBASE
ANSWERS '20-21' FROM FILE BIOTECHNO
ANSWERS '22-24' FROM FILE TOXCENTER
ANSWER '25' FROM FILE WPIDS
ANSWER '26' FROM FILE SCISEARCH
ANSWER '27' FROM FILE USPATFULL

> d iall 1-7; d ibib ed ab hitrn 8-11; d iall 12-26; d ibib ab hitrn 27; fil hom

39 ANSWER 1 OF 27 MEDLINE on STN DUPLICATE 5
CESSION NUMBER: 2002698171 MEDLINE
OCUMENT NUMBER: PubMed ID: 12459382
ITLE: Enhancement of vascular targeting by inhibitors of nitric
oxide synthase.
UTHOR: Davis Peter D; Tozer Gillian M; Naylor Matthew A; Thomson
Peter; Lewis Gemma; Hill Sally A
ORPORATE SOURCE: Angiogene Pharmaceuticals Ltd., England, Oxford, UK..
pdd@angiogene.co.uk
OURCE: International journal of radiation oncology, biology,
physics, (2002 Dec 1) 54 (5) 1532-6.
Journal code: 7603616. ISSN: 0360-3016.
JB. COUNTRY: United States
OCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
ANGUAGE: English
ILE SEGMENT: Priority Journals
NTRY MONTH: 200301
NTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030103
Entered Medline: 20030102

BSTRACT:
URPOSE: This study investigates the enhancement of the vascular targeting
ctivity of the **tubulin-binding** agent
combretastatin A4 phosphate (CA4P) by various inhibitors of
nitric oxide synthases. METHODS AND MATERIALS: The syngeneic tumors CaNT and
AS growing in CBA mice were used for this study. Reduction in perfused
ascular volume was measured by injection of Hoechst 33342 24 h after drug
ministration. Necrosis (hematoxylin and eosin stain) was assessed also at 24
after treatment. **Combretastatin A4** phosphate was
ynthesized by a modification of the published procedure and the nitric oxide
ynthase inhibitors L-NNA, L-NMMA, L-NIO, L-NIL, S-MTC, S-EIT, AMP, AMT, and

TC, obtained from commercial sources. RESULTS: A statistically significant augmentation of the reduction in perfused vascular volume by CA4P in the CaNT tumor was observed with L-NNA, AMP, and AMT. An increase in CA4P-induced necrosis in the same tumor achieved significance with L-NNA, L-NMMA, L-NIL, and T. CA4P induced little necrosis in the SaS tumor, but combination with the inhibitors L-NNA, L-NMMA, L-NIO, S-EIT, and L-TC was effective. CONCLUSIONS: Augmentation of CA4P activity by nitric oxide synthase inhibitors of different structural classes supports a nitric oxide-related mechanism for this effect. L-NNA was the most effective inhibitor studied.

CONTROLLED TERM: ***Angiogenesis Inhibitors: TU, therapeutic use**
 Animals
***Antineoplastic Agents, Phytogenic: TU, therapeutic use**
 Benzimidazoles: PD, pharmacology
***Enzyme Inhibitors: PD, pharmacology**
 Fluorescent Dyes: PD, pharmacology
 Mice
 Mice, Inbred CBA
 Models, Chemical
 Necrosis
***Neovascularization, Pathologic**
***Nitric-Oxide Synthase: AI, antagonists & inhibitors**
***Stilbenes: TU, therapeutic use**
 Time Factors
 Tubulin: ME, metabolism
 Tumor Cells, Cultured

S REGISTRY NO.: 117048-59-6 (combretastatin A-4); 23491-52-3 (HOE 33342)

CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents, Phytogenic); 0 (Benzimidazoles); 0 (Enzyme Inhibitors); 0 (Fluorescent Dyes); 0 (Stilbenes); 0 (Tubulin); EC 1.14.13.39 (Nitric-Oxide Synthase)

9 ANSWER 2 OF 27 MEDLINE on STN DUPLICATE 7

SESSION NUMBER: 2001482503 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11522635

TITLE: Mechanisms associated with tumor vascular shut-down induced by **combretastatin A-4** phosphate: intravital microscopy and measurement of vascular permeability.

AUTHOR: Tozer G M; Prise V E; Wilson J; Cemazar M; Shan S; Dewhirst M W; Barber P R; Vojnovic B; Chaplin D J

CORPORATE SOURCE: Gray Cancer Institute, Mount Vernon Hospital, Northwood, Middlesex, HA6 2JR, United Kingdom.. tozer@graylab.ac.uk

SOURCE: Cancer research, (2001 Sep 1) 61 (17) 6413-22.
 Journal code: 2984705R. ISSN: 0008-5472.

B. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

TRY MONTH: 200109

TRY DATE: Entered STN: 20010830
 Last Updated on STN: 20010917
 Entered Medline: 20010913

ABSTRACT:

The tumor vascular effects of the tubulin destabilizing agent disodium combretastatinA-4 3-O-phosphate (CA-4-P) were investigated in the rat P22 tumor growing in a dorsal skin flap window chamber implanted into BD9 rats. CA-4-P in clinical trial as a tumor vascular targeting agent. In animal tumors, it can cause the shut-down of blood flow, leading to extensive tumor cell necrosis. However, the mechanisms leading to vascular shut-down are still unknown. Tumor vascular effects were visualized and monitored on-line before

d after the administration of two doses of CA-4-P (30 and 100 mg/kg) using travital microscopy. The combined effect of CA-4-P and systemic nitric oxide nynthase (NOS) inhibition using N(omega)-nitro-L-arginine (L-NNA) was also sessed, because this combination has been shown previously to have a tentiating effect. The early effect of CA-4-P on tumor vascular permeability albumin was determined to assess whether this could be involved in the chanism of action of the drug. Tumor blood flow reduction was extremely pid after CA-4-P treatment, with red cell velocity decreasing throughout the servation period and dropping to <5% of the starting value by 1 h. NOS hibition alone caused a 50% decrease in red cell velocity, and the combined eatment of CA-4-P and NOS inhibition was approximately additive. The chanism of blood flow reduction was very different for NOS inhibition and -4-P. That of NOS inhibition could be explained by a decrease in vessel ameter, which was most profound on the arteriolar side of the tumor rculatation. In contrast, the effects of CA-4-P resembled an acute flammatory reaction resulting in a visible loss of a large proportion of the allest blood vessels. There was some return of visible vasculature at 1 h ter treatment, but the blood in these vessels was static or nearly so, and ny of the vessels were distended. The hematocrit within larger draining mor venules tended to increase at early times after CA-4-P, suggesting fluid ss from the blood. The stacking of red cells to form rouleaux was also a ommon feature, coincident with slowing of blood flow; and these two factors ould lead to an increase in viscous resistance to blood flow. Tumor vascular rmeability to albumin was increased to approximately 160% of control values 1 and 10 min after treatment. This could lead to an early decrease in tumor ood flow via an imbalance between intravascular and tissue pressures and/or a increase in blood viscosity as a result of increased hematocrit. These ults suggest a mechanism of action of CA-4-P in vivo. Combination of CA-4-P th a NOS inhibitor has an additive effect, which it may be possible to ploit therapeutically.

CONTROLLED TERM:

Check Tags: Male; Support, Non-U.S. Gov't

***Angiogenesis Inhibitors: PD, pharmacology**

Animals

***Antineoplastic Agents, Phytogenic: PD, pharmacology**

Capillary Permeability: DE, drug effects

***Carcinosarcoma: BS, blood supply**

Carcinosarcoma: DT, drug therapy

Carcinosarcoma: ME, metabolism

Drug Synergism

Enzyme Inhibitors: PD, pharmacology

Microscopy, Fluorescence: MT, methods

***Neoplasms, Experimental: BS, blood supply**

Neoplasms, Experimental: DT, drug therapy

Neoplasms, Experimental: ME, metabolism

***Neovascularization, Pathologic: DT, drug therapy**

Neovascularization, Pathologic: PP, physiopathology

Nitric Oxide: BI, biosynthesis

Nitric Oxide: PH, physiology

Nitric-Oxide Synthase: AI, antagonists & inhibitors

Nitroarginine: PD, pharmacology

Rats

***Stilbenes: PD, pharmacology**

AS REGISTRY NO.:

10102-43-9 (Nitric Oxide); 117048-59-6 (combretastatin A-4); 2149-70-4 (Nitroarginine)

HEMICAL NAME:

0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents, Phytogenic); 0 (Enzyme Inhibitors); 0 (Stilbenes); EC 1.14.13.39 (Nitric-Oxide Synthase)

89 ANSWER 3 OF 27

MEDLINE on STN

CESSION NUMBER:

2003466591 MEDLINE

OCUMENT NUMBER:

PubMed ID: 14528278

TITLE: Ocular neovascularization: a valuable model system.
 AUTHOR: Campochiaro Peter Anthony; Hackett Sean Francis
 CORPORATE SOURCE: Department of Ophthalmology, The Johns Hopkins University
 School of Medicine, Maumenee 719, 600 N. Wolfe Street,
 Baltimore, MD 21287-9277, USA.. pcampo@inmi.edu
 CONTRACT NUMBER: EY05951 (NEI)
 EY12609 (NEI)
 P30EY1765 (NEI)
 SOURCE: Oncogene, (2003 Sep 29) 22 (42) 6537-48. Ref: 133
 Journal code: 8711562. ISSN: 0950-9232.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, ACADEMIC)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200311
 ENTRY DATE: Entered STN: 20031008
 Last Updated on STN: 20031113
 Entered Medline: 20031112

ABSTRACT:
 There is no unique formula for angiogenesis. Instead there is a large group of potential participating proteins that interact in complex ways. Depending upon the surrounding cell types and the relative expression levels of angiogenesis-related proteins, the 'angiogenesis cascade' can vary. Therefore, it is valuable to study and compare the role of proteins in several well-characterized vascular beds. The eye provides a useful model system, because it contains several vascular beds sandwiched between avascular tissue. This allows for unequivocal identification and quantitation of new vessels. Retina-specific promoters combined with inducible promoter systems provide a means to regulate the expression of proteins of interest. As a relatively isolated compartment, the eye also provides advantages for gene transfer. By gaining insight regarding the molecular signals involved in various types of ocular angiogenesis, general concepts can emerge that may apply to other settings, including tumor angiogenesis. One concept that has emerged is that despite participation of multiple stimulatory factors for ocular neovascularization, VEGF plays an essential role and interruption of VEGF signaling is an important therapeutic strategy. Another concept is that while most studies have focused on prevention of ocular neovascularization, regression of new vessels is desirable and is achievable with at least three agents, **combretastatin A-4** phosphate, pigment epithelium-derived factor, and angiopoietin-2. Finally, endostatin and angiostatin, which have been sources of controversy because of inconsistent results in tumor models, have been shown to have good efficacy when delivered by gene transfer in models of ocular neovascularization. These results provide leads for new ocular treatments and perspective for evaluation of studies of neovascularization in extraocular tissues.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Angiogenesis Inhibitors: TU, therapeutic use
 Animals
 Choroid: BS, blood supply
 Disease Models, Animal
 Endothelial Growth Factors: PH, physiology
 Enzyme Inhibitors: TU, therapeutic use
 *Eye: BS, blood supply
 Intercellular Signaling Peptides and Proteins: PH, physiology
 Lymphokines: PH, physiology
 Mice
 Models, Biological
 Neovascularization, Pathologic: DT, drug therapy

*Neovascularization, Pathologic: GE, genetics
*Neovascularization, Pathologic: PA, pathology
Nitric-Oxide Synthase: AI, antagonists & inhibitors

*Retinal Vessels: PA, pathology
Vascular Endothelial Growth Factor A
Vascular Endothelial Growth Factors

CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Endothelial Growth Factors); 0 (Enzyme Inhibitors); 0 (Intercellular Signaling Peptides and Proteins); 0 (Lymphokines); 0 (Vascular Endothelial Growth Factor A); 0 (Vascular Endothelial Growth Factors); EC 1.14.13.39 (Nitric-Oxide Synthase)

L89 ANSWER 4 OF 27 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 6
ACCESSION NUMBER: 2002-24213 DRUGU P
TITLE: Importance of tumor size and nitric oxide levels in determining tumor sensitivity to **combretastatin A-4** disodium phosphate.
AUTHOR: Murata R; Horsman M R
LOCATION: Aarhus, Den.
SOURCE: Proc.Am.Assoc.Cancer Res. (43, 93 Meet., 157, 2002) ISS
N: 0197-016X
AVAIL. OF DOC.: Danish Cancer Society, Dept. Experimental Clinical Oncology, Aarhus, Denmark.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

Although the novel vascular targeting drug i.p. **combretastatin A-4** disodium phosphate (CA4DP) induces vascular damage in a wide spectrum of tumor models the degree of activity can be highly variable. The aim of this study was to investigate some of the important factors that may determine this activity in 2 murine tumor models. C3H mammary carcinoma showed no size dependent response to CA4DP and was generally less response to the vascular damaging agent than the KHT sarcoma that did show a tumor size dependency. Interestingly, the response of both tumor types could be substantially improved by **inhibiting nitric oxide** production by co-administration of l.v. nitro-L-arginine (NLA). (conference abstract: 93rd Annual Meeting of the American Association for Cancer Research, San Francisco, California, USA, 2002).

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 52 Chemotherapy - non-clinical
66 Drug Interactions

CONTROLLED TERM:

C3H *OC; MAMMA *OC; MAMMA-DISEASE *OC; CARCINOMA *OC; KHT *OC; SARCOMA *OC; ANIMAL-NEOPLASM *OC; MOUSE *FT; IN-VIVO *FT; ATHYMIC *FT; NUDE *FT; COMB. *FT; NITRIC-OXIDE *FT; LAB.ANIMAL *FT

[01]

COMBRETASTATIN-A-4 *PH;
COMBRETASTATIN-A-4 *DI; PHOSPHATE
*DI; PHOSPHATE *PH; NITROARGININE-N-G *DI; SODIUM *PH; SODIUM *DI; COMBRESA4 *RN; SODIUM-SALT *FT; CYTOSTATIC *FT; ANGIOGENESIS-INHIBITOR *FT; I.P. *FT; ALONE *FT; INJECTION *FT; CYTOSTATICS *FT; ANGIOGENESIS-INHIBITORS *FT; PH *FT; DI *FT

CAS REGISTRY NO.: 117048-59-6

[02]

NITROARGININE-N-G *PH; NITROARGININE-N-G *DI;
COMBRETASTATIN-A-4 *DI; NOARG-N-G

*RN; SYNERGIST *FT; **NITRIC-OXIDE**
-SYNTHASE-INHIBITOR *FT; I.V. *FT; INJECTION *FT;
NITRIC-OXIDE-SYNTHASE-INHIBITORS
*FT; PH *FT; DI *FT

CAS REGISTRY NO.: **2149-70-4**
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L89 ANSWER 5 OF 27 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 9
ACCESSION NUMBER: 2000-38636 DRUGU P
TITLE: Determinants of anti-vascular action by
combretastatin A.4 phosphate:
role of nitric oxide.
AUTHOR: Parkins C S; Holder A L; Hill S A; Chaplin D J; Tozer G M
CORPORATE SOURCE: Aventis
LOCATION: Northwood, U.K.; Vitry- Alfortville; Vitry sur Seine, Fr.
SOURCE: Br.J.Cancer (83, No. 6, 811-16, 2000) 4 Fig. 33 Ref.
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Tumour Microcirculation Group, Gray Laboratory Cancer
Research Trust, Mount Vernon Hospital, Northwood, Middlesex,
HA6 2JR, England.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

The antivasular action of i.p. **combretastatin A-4**
-phosphate Na₂ (CA-4-P, Oxigene) was determined in mice bearing breast CaNT
adenocarcinoma and round cell SaS sarcoma cells. Simultaneous administration
of CA-4-P with nitroarginine-N-G (Sigma-Chem.) resulted in enhanced vascular
damage and cytotoxicity in both tumor types. NO was shown to modify the tumor
vascular damage induced by CA-4-P. This appeared to be due to tumor-dependent
levels of NO acting to reduce the tumor infiltration of neutrophils, thereby
reducing the damage to the tumor vascular endothelium after CA-4-P. The
understanding of the role of NO in tumor vascular infiltration is important
both for the development of CA-4-P as a cancer chemotherapeutic agent and for
the future development of new vascular targeting agents.

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 52 Chemotherapy - non-clinical
66 Drug Interactions

CONTROLLED TERM:

SARCOMA *OC; ADENOCARCINOMA *OC; MAMMA *OC; MAMMA-DISEASE
*OC; ANIMAL-NEOPLASM *OC; MOUSE *FT; IN-VIVO *FT; I.P. *FT;
CYTOSTATIC *FT; NEUTROPHIL *FT; NITRIC-OXIDE *FT;
FREE-RADICAL *FT; VESSEL *FT; FUNCTION *FT; COMB. *FT;
LAB.ANIMAL *FT; INJECTION *FT; LEUKOCYTE *FT
[01] **COMBRETASTATIN-A-4** *PH;
COMBRETASTATIN-A-4 *DI; PHOSPHATE
*PH; NITROARGININE-N-G *DI; COMBRESA4 *RN; OXIGENE *FT;
MODE-OF-ACT. *FT; CYTOSTATICS *FT; ANGIOGENESIS-INHIBITORS
*FT; PH *FT; DI *FT

CAS REGISTRY NO.: **117048-59-6**
[02] NITROARGININE-N-G *PH; NITROARGININE-N-G *DI; SIGMA-CHEM.
*FT; **COMBRETASTATIN-A-4** *DI;
NOARG-N-G *RN; **NITRIC-OXIDE-SYNTHASE-**
INHIBITOR *FT; **NITRIC-OXIDE**
-SYNTHASE-INHIBITORS *FT; PH *FT; DI *FT

CAS REGISTRY NO.: **2149-70-4**
FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

L89 ANSWER 6 OF 27 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2002-11176 DRUGU P G

TITLE: Enhancement of **combretastatin A4**
phosphate activity by **nitric oxide**
synthase **inhibitors** of different structural
classes.AUTHOR: Davis P D; Thomson P; Naylor M A; Nolan J; Lewis G S; Hill S
A

CORPORATE SOURCE: Angiogene; Gray-Lab.Cancer-Res.Trust

LOCATION: Aston Rowant; Northwood, U.K.

SOURCE: Clin.Cancer Res. (7, Suppl., 3656S, 2001)

CODEN: CCREF ISSN: 1078-0432

AVAIL. OF DOC.: Angiogene Pharmaceuticals Ltd, Aston Rowant, England.

LANGUAGE: English

DOCUMENT TYPE: Journal

ABSTRACT:

Combretastatin A4 phosphate (CA4P) reduced vascular volume in mice bearing CaNT tumors. The NOS inhibitors L-nitroarginine (L-NNA), AMT and AMP enhanced the vascular volume reduction by CA4P. The induction of tumor necrosis by CA4P was also enhanced both in CaNT and SaS tumors. ANG-500, designed to give provide both combrestatin A4 and L-NNA by cleavage after in vivo administration, was more potent than CA4P against the CaNT tumor in reduction of vascular volume, induction of necrosis and reduction in surviving fraction per gram. Growth delay was achieved with a single dose of ANG-500. The vascular targeting activity of CA4P can be enhanced by NOS inhibitors of different structural classes. (conference abstract: AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Miami Beach, Florida, USA, 2001).

SECTION HEADING: P Pharmacology
G GalenicsCLASSIF. CODE: 29 Pharmaceutics
52 Chemotherapy - non-clinical
65 Drug Delivery
66 Drug Interactions
72 New Drugs
73 Trial Preparations

CONTROLLED TERM:

[01] ANIMAL-NEOPLASM *OC; IN-VIVO *FT; MOUSE *FT; NECROSIS *FT;
VESSEL *FT; BIOPHARM. *FT; LAB.ANIMAL *FT
COMBRETASTATIN-A-4 *PH;
COMBRETASTATIN-A-4 *DI;
NITROARGININE-N-G *DI; COMBRESA4 *RN; CYTOSTATIC *FT;
ANGIOGENESIS-INHIBITOR *FT; COMB. *FT; ALONE *FT; CYTOSTATICS
*FT; ANGIOGENESIS-INHIBITORS *FT; PH *FT; DI *FT

CAS REGISTRY NO.: 117048-59-6

[02] NITROARGININE-N-G *PH; NITROARGININE-N-G *DI;
COMBRETASTATIN-A-4 *DI; NOARG-N-G
*RN; **NITRIC-OXIDE-SYNTHASE-**
INHIBITOR *FT; SYNERGIST *FT; COMB. *FT; ALONE *FT;
NITRIC-OXIDE-SYNTHASE-INHIBITORS
*FT; PH *FT; DI *FT

CAS REGISTRY NO.: 2149-70-4

[03] ANG-500 *PH; DR0059221 *RN; PRODRUG *FT; ANGIOGENESIS-
INHIBITOR *FT; CYTOSTATIC *FT; **NITRIC-OXIDE**
-SYNTHASE-INHIBITOR *FT; SINGLE *FT; DOSAGE *FT;

NEW *FT; TRIAL-PREP. *FT; **NITRIC-OXIDE**
-SYNTHASE-INHIBITORS *FT; CYTOSTATICS *FT;
ANGIOGENESIS-INHIBITORS *FT; BIOPHARM. *FT; PH *FT
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L89 ANSWER 7 OF 27 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-04124 DRUGU P
TITLE: Tumor nitric oxide levels and vascular targeting with
combretastatin A-4-P.
AUTHOR: Tozer G M; Prise V E; Wilson I
CORPORATE SOURCE: Gray-Lab.Cancer-Res.
LOCATION: Northwood, U.K.
SOURCE: Proc.Am.Assoc.Cancer Res. (42, 92 Meet., 824, 2001) ISS
N: 0197-016X
AVAIL. OF DOC.: Gray Laboratory Cancer Research Trust, Middlesex, England.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

I.p. **combretastatin A4-P** (CA-4-P) reduced tumor blood flow in rats bearing subcutaneous P22 tumors. L-NNA and its pro-drug L-NAME, selectively reduced tumor blood flow. Combined chronic p.o. and i.p. L-NAME and CA-4-P produced a more than additive effect in the tumor. Acute inhibition of NOS at the time of CA-4-P administration had no more than an additive effect. Constitutively produced nitric oxide synthase (NOS), rather than inducible NOS (iNOS) has an important role in the maintenance of blood flow in the P22 tumor. A vascular effect of chronic NOS inhibition, rather than acute tumor blood flow reduction at the time of CA-4-P administration, sensitizes the tumor vasculature to the damaging effects of CA-4-P. This combination may be therapeutically useful. (conference abstract: 92nd Annual Meeting of the American Association for Cancer Research, New Orleans, Louisiana, USA, 2001).

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 8 Pharmacokinetics
52 Chemotherapy - non-clinical
66 Drug Interactions

CONTROLLED TERM:

P22 *OC; ANIMAL-NEOPLASM *OC; IN-VIVO *FT; I.P. *FT; RAT *FT;
BLOOD-FLOW *FT; ALONE *FT; COMB. *FT; EC-1.14.13.39 *FT;
INJECTION *FT; LAB.ANIMAL *FT; HEMODYNAMICS *FT;
NITRIC-OXIDE-SYNTHASE *FT
[01] **COMBRETASTATIN-A-4** *PH;
COMBRETASTATIN-A-4 *DM;
NITROARGININE-N-G-METHYLESTER *DI; NITROARGININE-N-G *DI;
COMBRESA4 *RN; CYTOSTATIC *FT; CYTOSTATICS *FT;
ANGIOGENESIS-INHIBITORS *FT; PH *FT; DM *FT

CAS REGISTRY NO.: 117048-59-6

[02] NITROARGININE-N-G-METHYLESTER *PH; NITROARGININE-N-G-METHYLESTER *DM; NITROARGININE-N-G-METHYLESTER *DI;
COMBRETASTATIN-A-4 *DI; NO2ARGMEE
*RN; PRODRUG *FT; BIOSYNTH. *FT; P.O. *FT; **NITRIC-OXIDE-SYNTHASE-INHIBITOR** *FT; ACUTE *FT;
CHRON. *FT; DOSAGE *FT; BIOPHARM. *FT; VASOCONSTRICTORS *FT;
NITRIC-OXIDE-SYNTHASE-INHIBITORS
*FT; PH *FT; DM *FT; DI *FT

[03] NITROARGININE-N-G *PH; NITROARGININE-N-G *DM;
NITROARGININE-N-G *DI; **COMBRETASTATIN-A-4** *DI; NOARG-N-G *RN; PRODRUG *FT; **NITRIC-**

OXIDE-SYNTHASE-INHIBITOR *FT; BIOPHARM.
 *FT; **NITRIC-OXIDE-SYNTHASE-**
INHIBITORS *FT; PH *FT; DM *FT; DI *FT

CAS REGISTRY NO.: 2149-70-4
 FIELD AVAIL.: AB; LA; CT
 FILE SEGMENT: Literature

L89 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8
 ACCESSION NUMBER: 2000:592549 CAPLUS
 DOCUMENT NUMBER: 133:172166
 TITLE: Combinations for the treatment of diseases involving
 angiogenesis
 INVENTOR(S): Davis, Peter David
 PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
 SOURCE: PCT Int. Appl., 18 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048591	A1	20000824	WO 2000-GB511	20000215
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000008254	A	20011106	BR 2000-8254	20000215
EP 1161235	A1	20011212	EP 2000-903832	20000215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537251	T2	20021105	JP 2000-599383	20000215
NZ 513429	A	20031031	NZ 2000-513429	20000215
ZA 2001006688	A	20020814	ZA 2001-6688	20010814
NO 2001003966	A	20011015	NO 2001-3966	20010815
PRIORITY APPLN. INFO.:			GB 1999-3404	A 19990216
			WO 2000-GB511	W 20000215

ED Entered STN: 25 Aug 2000
 AB Compns. for the inhibition of the formation of new vasculature by
 angiogenesis are provided comprising the combination of a vasculature
 damaging agent and an inhibitor of the formation or action of nitric oxide
 in mammalian systems. An example is given showing enhancement of
 combretastatin A4 phosphate activity in SaS tumors by coadministration of
 L-NG-nitroarginine.
 IT 695-34-1, 2-Amino-4-methylpyridine 2149-70-4,
 L-NG-Nitroarginine 17035-90-4 222030-63-9
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
 (Uses)
 (combinations for the treatment of diseases involving angiogenesis)
 IT 36889-13-1 53774-63-3 57444-72-1
 156719-37-8, L-Thiocitrulline 156719-38-9,
 L-Homothiocitrulline 156719-41-4, S-Methyl-L-thiocitrulline

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations for the treatment of diseases involving angiogenesis)

IT 10102-43-9, Nitric oxide, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; combinations for the treatment of diseases
involving angiogenesis)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:142717 CAPLUS

DOCUMENT NUMBER: 136:183937

TITLE: Preparation and use of cis-stilbene derivatives with
vascular damaging activity

INVENTOR(S): Davis, Peter David

PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK

SOURCE: PCT Int. Appl., 21 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002014329	A1	20020221	WO 2001-GB3668	20010815
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2001077629	A5	20020225	AU 2001-77629	20010815
EP 1311514	A1	20030521	EP 2001-955467	20010815
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
US 2003181424	A1	20030925	US 2003-367606	20030214
PRIORITY APPLN. INFO.:			GB 2000-19944 A	20000815
			WO 2001-GB3668 W	20010815

OTHER SOURCE(S): MARPAT 136:183937

ED Entered STN: 22 Feb 2002

AB The invention describes the prepn. of compns. which contain salts comprising, as an acidic component, compd. [I, wherein: R1, R2 and R3, independently = alkyl; R4 = alkoxy, haloalkoxy, alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulfonyl, hydroxy, halo; R5 = H, alkoxy, alkyl, alkylthio, hydroxy, phosphate or halo]; and, as the basic component, a compd. selected from the group consisting of compd. [II, wherein: R6 = H, alkyl; R7 = alkyl, alkylamino, dialkylamino, nitroamino, hydrazine, mercapto, alkylthio; X = CH2, CH2CH2, CH2S, CH2CH2S; Y = NH, S], or compd. [III, wherein: R8 = alkyl, aminoalkyl; R9 = H, alkyl, or optionally substituted Ph], or compd. [IV, wherein: Z = O, S, CH2, CHR13, or a bond; R10, R11, R12 and R13, independently = H, alkyl], or compd. [V, wherein: R14 = alkyl], and the pharmaceutically acceptable solvates and hydrates thereof. Thus, a mixt. of combretastatin A4 phosphate and L-NG-nitroarginine Me ester was dissolved in water, stirred for 18 h, and freeze-dried to produce (Z)-2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di(1-methoxycarbonyl-4-N'-nitroguanidinobutylammonium) phosphate. The prepd. compns. are useful as antitumor agents, and are angiogenesis inhibitors displaying vascular

damaging activity. Biol. data are given.

IT 222030-63-9

RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use);
BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(prepn. and use of cis-stilbene derivs. with vascular damaging
activity)

IT 2149-70-4

RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. and use of cis-stilbene derivs. with vascular damaging
activity)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:592548 CAPLUS

DOCUMENT NUMBER: 133:177486

TITLE: Preparation of substituted stilbene compounds with
vascular damaging activity

INVENTOR(S): Davis, Peter David

PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK

SOURCE: PCT Int. Appl., 31 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048590	A1	20000824	WO 2000-GB503	20000215
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1154767	A1	20011121	EP 2000-903824	20000215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537250	T2	20021105	JP 2000-599382	20000215
PRIORITY APPLN. INFO.: GB 1999-3403 A 19990216				
WO 2000-GB503 W 20000215				

OTHER SOURCE(S): MARPAT 133:177486

ED Entered STN: 25 Aug 2000

AB A vascular damaging agent AXB (A = substituted cis-stilbene; X = linker bond, atom, or group; B = moiety derived from an inhibitor of the formation or action of NO in mammalian systems), is claimed. Thus, (Z)-1-[3-(N-.alpha.-tert-butoxycarbonyl-N-.omega.-nitroarginyloxy)-4-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)ethene was stirred with CF₃CO₂H in CH₂Cl₂ to give (Z)-1-(4-methoxy-3-NG-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene. The latter at 50 mg/kg i.p. in mice bearing CaNT or SaS tumors gave 95% redn. in vascular vol. and 91-100% tumor necrosis.

IT 125978-95-2, Nitric oxide synthase

RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)

(inhibitors; prepn. of substituted stilbene compds. with
vascular damaging activity)

IT 117048-59-6

RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of substituted stilbene compds. with vascular damaging activity)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 11 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1984:622096 CAPLUS

DOCUMENT NUMBER: 101:222096

TITLE: Functional group contributions to drug-receptor interactions

AUTHOR(S): Andrews, P. R.; Craik, D. J.; Martin, J. L.

CORPORATE SOURCE: Victorian Coll. Pharm. Ltd., Parkville, 3052, Australia

SOURCE: Journal of Medicinal Chemistry (1984), 27(12), 1648-57
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 22 Dec 1984

AB To overcome the difficulties in estg. the potential bond strengths involved in the interaction between a drug and a reasonable matched receptor, 200 drugs and enzyme inhibitors chosen on the basis of their apparent tight binding to their corresponding receptor sites, were used to provide a statistical est. of the strength of noncovalent bonds assocd. with each functional groups in an av. drug-receptor environment. Values are presented to det. the goodness of fit of a drug to its receptor by comparing the obsd. binding const. to the av. binding energy calcd. by summing the intrinsic binding energies of the component groups and then subtracting 2 entropy related terms. Drugs such as diazepam [439-14-5] that match their receptors well have a measured binding energy exceeding the calcd. av. value, whereas others such as buprenorphine [52485-79-7] who match their receptor less than the av. have binding energies less the calcd. av. value. In addn. the binding energies of 3 central nervous system active drugs and representative amino acids within a polypeptide mol. are also given. General principles for the application of intrinsic binding energies in drug design and structure-activity relations are discussed.

IT 56-87-1, biological studies 38838-26-5

RL: PROC (Process)

(binding of, with receptors)

L89 ANSWER 12 OF 27 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2

ACCESSION NUMBER: 2003:153852 BIOSIS

DOCUMENT NUMBER: PREV200300153852

TITLE: The First International Conference on Vascular Targeting: Meeting overview.

AUTHOR(S): Thorpe, Philip E. [Reprint Author]; Chaplin, David J.; Blakey, David C.

CORPORATE SOURCE: Department of Pharmacology, University of Texas
Southwestern Medical Center, Dallas, TX, 75390, USA
philip.thorpe@utsouthwestern.edu

SOURCE: Cancer Research, (March 1 2003) Vol. 63, No. 5, pp. 1144-1147. print.
ISSN: 0008-5472 (ISSN print).

DOCUMENT TYPE: Article
Conference; Report; (Meeting Report)

LANGUAGE: English

ENTRY DATE: Entered STN: 26 Mar 2003

Last Updated on STN: 26 Mar 2003

ABSTRACT: The First International Conference on Vascular Targeting focused on vascular targeting agents (VTAs) that occlude or destroy the pre-existing blood vessels of solid tumors. The VTAs cause a rapid shutdown in the blood supply to the tumor that kills tumor cells by depriving them of oxygen and nutrients. The VTAs are distinct from antiangiogenic agents, which prevent new blood vessel formation. Two major types of VTAs are being developed for cancer: the ligand-directed VTAs that use antibodies, peptides, and growth factors to deliver toxins, procoagulants, and proapoptotic effectors to tumor endothelium, and the small molecule VTAs that do not specifically localize to tumor endothelium but exploit pathophysiological differences between tumor and normal tissue endothelia to induce acute vascular shutdown in tumors. Both approaches were described at the meeting and highlighted the variety of VTAs in preclinical development, their selectivity for tumor endothelium, their rapid antitumor effects, and the improved activity seen when combined with other anticancer approaches (antiproliferative chemotherapeutic drugs, radiation, radiolabeled antibodies, **nitric oxide synthetase inhibitors**, and anti-angiogenic agents). Early clinical studies were summarized for the small molecule VTAs: the antitubulin drugs, **combreastatin**, **A4 phosphate (CA4P)** and **ZD6126**, and the flavonoid, **5,6-dimethylxanthone-4-acetic acid (DMXAA)**. The agents lacked the bone marrow and gastrointestinal toxicities associated with antiproliferative chemotherapy. As a marker of biological effect, blood flow reductions in tumors were measured using magnetic resonance imaging or positron emission tomography for all of the agents tested, and single-agent clinical activity was seen. These agents are now being evaluated in combined modality studies to see whether the impressive results obtained in experimental models can be translated into humans.

CONCEPT CODE:

- Biochemistry studies - General 10060
- Pathology - Therapy 12512
- Digestive system - Pathology 14006
- Cardiovascular system - Physiology and biochemistry 14504
- Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
- Pharmacology - General 22002
- Pharmacology - Clinical pharmacology 22005
- Pharmacology - Cardiovascular system 22010
- Toxicology - General and methods 22501
- Toxicology - Pharmacology 22504
- Neoplasms - Pathology, clinical aspects and systemic effects 24004
- Neoplasms - Therapeutic agents and therapy 24008
- Neoplasms - Blood and reticuloendothelial neoplasms 24010

INDEX TERMS:

- Major Concepts
 - Cardiovascular System (Transport and Circulation);
 - Pharmacology; Tumor Biology
- Parts, Structures, & Systems of Organisms
 - blood vessels: circulatory system, formation;
 - endothelium
- Diseases
 - bone marrow toxicity: blood and lymphatic disease,
 - toxicity, drug-induced
- Diseases
 - cancer: neoplastic disease, drug therapy
 - Neoplasms (MeSH)
- Diseases
 - gastrointestinal toxicity: digestive system disease,
 - toxicity, drug-induced
- Diseases
 - nonmalignant disease: disease-miscellaneous
- Chemicals & Biochemicals
 - 5,6-dimethylxanthone-4-acetic acid [DMXAA]:
 - antineoplastic-drug, cardiovascular-drug, clinical

trial; ZD6126: antineoplastic-drug, cardiovascular-drug, clinical trial; antiangiogenic agents: cardiovascular-drug; antiproliferative chemotherapeutic drugs: antineoplastic-drug; **combretastatin A4** phosphate: antineoplastic-drug, cardiovascular-drug, clinical trial; flavonoids: antineoplastic-drug, cardiovascular-drug; **nitric oxide synthase inhibitors**: enzyme inhibitor-drug; radiolabeled antibodies; tubulin-binding agents: antineoplastic-drug, cardiovascular-drug; vascular targeting agents: antineoplastic-drug, cardiovascular-drug

INDEX TERMS: Methods & Equipment
magnetic resonance imaging: clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques; positron emission tomography: clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques; radiation therapy: clinical techniques, therapeutic and prophylactic techniques

INDEX TERMS: Miscellaneous Descriptors
blood flow reduction; vascular targeting

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common): animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 117570-53-3 (5,6-dimethylxanthenone-4-acetic acid)
117570-53-3 (DMXAA)
219923-05-4 (ZD6126)
222030-63-9 (**combretastatin A4** phosphate)

L89 ANSWER 13 OF 27 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 10
ACCESSION NUMBER: 1999:225372 BIOSIS
DOCUMENT NUMBER: PREV199900225372
TITLE: **Combretastatin A-4** phosphate
as a tumor vascular-targeting agent: Early effects in tumors and normal tissues.

AUTHOR(S): Tozer, Gillian M. [Reprint author]; Prise, Vivien E.; Wilson, John; Locke, Rosalind J.; Vojnovic, Borivoj; Stratford, Michael R. L.; Dennis, Madeleine F.; Chaplin, David J.

CORPORATE SOURCE: Tumor Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, Middlesex, HA6 2JR, UK

SOURCE: Cancer Research, (April 1, 1999) Vol. 59, No. 7, pp. 1626-1634. print.

CODEN: CNREA8. ISSN: 0008-5472.

DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jun 1999
Last Updated on STN: 7 Jun 1999

ABSTRACT:The potential for tumor vascular-targeting by using the tubulin destabilizing agent disodium **combretastatin A-4** 3-0-phosphate (CA-4-P) was assessed in a rat system. This approach aims to shut down the established tumor vasculature, leading to the development of extensive tumor cell necrosis. The early vascular effects of CA-4-P were assessed in the s.c. implanted P22 carcinosarcoma and in a range of normal tissues. Blood flow was measured by the uptake of radiolabeled iodoantipyrine, and quantitative autoradiography was used to measure spatial heterogeneity of blood flow in tumor sections. CA-4-P (100 mg/kg i.p.) caused a significant increase in mean arterial blood pressure at 1 and 6 h after treatment and a very large decrease in tumor blood flow, which-by 6 h-was reduced approximately 100-fold. The spleen was the most affected normal tissue with a 7-fold reduction in blood flow at 6 h. Calculations of vascular resistance revealed some vascular changes in the heart and kidney for which there were no significant changes in blood flow. Quantitative autoradiography showed that CA-4-P increased the spatial heterogeneity in tumor blood flow. The drug affected peripheral tumor regions less than central regions. Administration of CA-4-P (30 mg/kg) in the presence of the **nitric oxide** synthase **inhibitor**, Nomega-nitro-L-arginine methyl ester, potentiated the effect of CA-4-P in tumor tissue. The combination increased tumor vascular resistance 300-fold compared with less than 7-fold for any of the normal tissues. This shows that tissue production of nitric oxide protects against the damaging vascular effects of CA-4-P. Significant changes in tumor vascular resistance could also be obtained in isolated tumor perfusions using a cell-free perfusate, although the changes were much less than those observed in vivo. This shows that the action of CA-4-P includes mechanisms other than those involving red cell viscosity, intravascular coagulation, and neutrophil adhesion. The uptake of CA-4-P and **combretastatin A-4** (CA-4) was more efficient in tumor than in skeletal muscle tissue and dephosphorylation of CA-4-P to CA-4 was faster in the former. These results are promising for the use of CA-4-P as a tumor vascular-targeting agent.

CONCEPT CODE: Neoplasms - General 24002
Cytology - Animal 02506
Biochemistry studies - General 10060
Metabolism - General metabolism and metabolic pathways 13002
Cardiovascular system - General and methods 14501
Blood - General and methods 15001
Urinary system - General and methods 15501
Muscle - General and methods 17501
General biology - Miscellaneous 00532

INDEX TERMS: Major Concepts
Biochemistry and Molecular Biophysics; Tumor Biology

INDEX TERMS: Parts, Structures, & Systems of Organisms
heart: circulatory system; kidney: excretory system;
skeletal muscle: muscular system; spleen: blood and lymphatics, immune system

INDEX TERMS: Chemicals & Biochemicals
combretastatin A-4
phosphate: dephosphorylation, tumor vascular-targeting agent, uptake; nitric oxide: production

INDEX TERMS: Miscellaneous Descriptors
mean arterial blood pressure; tumor blood flow; vascular resistance

ORGANISM: Classifier
Cricetidae 86310
Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 P22 cell line: rat carcinosarcoma cell
 Taxa Notes
 Animals, Chordates, Mammals, Nonhuman Vertebrates,
 Nonhuman Mammals, Rodents, Vertebrates
 ORGANISM: Classifier
 Muridae 86375
 Super Taxa
 Rodentia; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 rat: animal model
 Taxa Notes
 Animals, Chordates, Mammals, Nonhuman Vertebrates,
 Nonhuman Mammals, Rodents, Vertebrates
 REGISTRY NUMBER: 10102-43-9 (nitric oxide)
 14265-44-2 (PHOSPHATE)
 82855-09-2 (COMBRETASTATIN)

L89 ANSWER 14 OF 27 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN DUPLICATE 1

ACCESSION NUMBER: 2003453009 EMBASE
 TITLE: Ocular neovascularization: A valuable model system.
 AUTHOR: Campochiaro P.A.; Hackett S.F.
 CORPORATE SOURCE: P.A. Campochiaro, Depts. of Ophthalmol. and Neurosci.,
 Johns Hopkins Univ. Sch. of Medicine, Maumenee 719, 600 N.
 Wolfe Street, Baltimore, MD 21287-9277, United States.
 pcampo@inmi.edu
 SOURCE: Oncogene, (2 Oct 2003) 22/43 (6537-6548).
 Refs: 133
 ISSN: 0950-9232 CODEN: ONCNES
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 005 General Pathology and Pathological Anatomy
 012 Ophthalmology
 016 Cancer
 030 Pharmacology
 037 Drug Literature Index
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ABSTRACT:
 There is no unique formula for angiogenesis. Instead there is a large group of potential participating proteins that interact in complex ways. Depending upon the surrounding cell types and the relative expression levels of angiogenesis-related proteins, the 'angiogenesis cascade' can vary. Therefore, it is valuable to study and compare the role of proteins in several well-characterized vascular beds. The eye provides a useful model system, because it contains several vascular beds sandwiched between avascular tissue. This allows for unequivocal identification and quantitation of new vessels. Retina-specific promoters combined with inducible promoter systems provide a means to regulate the expression of proteins of interest. As a relatively isolated compartment, the eye also provides advantages for gene transfer. By gaining insight regarding the molecular signals involved in various types of ocular angiogenesis, general concepts can emerge that may apply to other settings, including tumor angiogenesis. One concept that has emerged is that despite participation of multiple stimulatory factors for ocular neovascularization, VEGF plays an essential role and interruption of VEGF signaling is an important therapeutic strategy. Another concept is that while most studies have focused on prevention of ocular neovascularization, regression of new vessels is desirable and is achievable with at least three agents, combretastatin A-4 phosphate, pigment epithelium-derived factor, and angiopoietin-2. Finally, endostatin and angiostatin, which have been sources of

controversy because of inconsistent results in tumor models, have been shown to have good efficacy when delivered by gene transfer in models of ocular neovascularization. These results provide leads for new ocular treatments and perspective for evaluation of studies of neovascularization in extraocular tissues.

CONTROLLED TERM:

Medical Descriptors:

*retina macula age related degeneration: ET, etiology
 *retina neovascularization: DT, drug therapy
 *retina neovascularization: ET, etiology
 *subretinal neovascularization: DT, drug therapy
 *subretinal neovascularization: ET, etiology
 retinopathy: ET, etiology
 retina macula degeneration: ET, etiology
 neovascularization (pathology): DT, drug therapy
 neovascularization (pathology): ET, etiology
 signal transduction
 transgenic mouse
 colorectal cancer: ET, etiology
 colorectal cancer: PC, prevention
 thyroid cancer: DT, drug therapy
 cancer: DT, drug therapy
 cancer: ET, etiology
 cancer: PC, prevention
 angiogenesis
 enzyme inhibition
 gene transfer
 isotope labeling
 human
 nonhuman
 mouse
 clinical article
 clinical trial
 animal model
 review
 priority journal

Drug Descriptors:

*vasculotropin
 *pigment epithelium derived factor
 *combretastatin A4: CT, clinical trial
 *combretastatin A4: AD, drug administration
 *combretastatin A4: DO, drug dose
 *combretastatin A4: DT, drug therapy
 *combretastatin A4: PD, pharmacology
 *combretastatin A4: IP, intraperitoneal drug administration
 *vasculotropin antibody: CT, clinical trial
 *vasculotropin antibody: AD, drug administration
 *vasculotropin antibody: DT, drug therapy
 *vasculotropin antibody: PK, pharmacokinetics
 *vasculotropin antibody: VI, intravitreal drug administration
 *nepafenac: AD, drug administration
 *nepafenac: PK, pharmacokinetics
 *nepafenac: PD, pharmacology
 *nepafenac: TP, topical drug administration
 vasculotropin receptor
 rhodopsin
 receptor subtype
 complementary DNA
 messenger RNA
 growth hormone

somatomedin C
 fibroblast growth factor 2: EC, endogenous compound
 angiopoietin 1
 angiopoietin 2
 iodine 125
 immunoglobulin F(ab')₂ fragment
 human monoclonal antibody: CT, clinical trial
 human monoclonal antibody: AD, drug administration
 human monoclonal antibody: DT, drug therapy
 human monoclonal antibody: PK, pharmacokinetics
 human monoclonal antibody: VI, intravitreal drug
 administration
 nonsteroid antiinflammatory agent: PD, pharmacology
 cyclooxygenase 1 inhibitor: AD, drug administration
 cyclooxygenase 1 inhibitor: PK, pharmacokinetics
 cyclooxygenase 1 inhibitor: PD, pharmacology
 cyclooxygenase 1 inhibitor: TP, topical drug administration
 cyclooxygenase 2 inhibitor: AD, drug administration
 cyclooxygenase 2 inhibitor: PK, pharmacokinetics
 cyclooxygenase 2 inhibitor: PD, pharmacology
 cyclooxygenase 2 inhibitor: TP, topical drug administration
 nitric oxide synthase: AD, drug administration
 nitric oxide synthase: DT, drug therapy
 nitric oxide synthase: PD, pharmacology
 nitric oxide synthase: PO, oral drug administration
 n(g) methylarginine: AD, drug administration
 n(g) methylarginine: DT, drug therapy
 n(g) methylarginine: PD, pharmacology
 n(g) methylarginine: PO, oral drug administration
 monoclonal antibody lm 609: CT, clinical trial
 monoclonal antibody lm 609: DT, drug therapy
 monoclonal antibody lm 609: PD, pharmacology
 proteinase inhibitor: DT, drug therapy
 proteinase inhibitor: PD, pharmacology
 plasminogen activator inhibitor 1: EC, endogenous compound
 tissue inhibitor of metalloproteinase 1: EC, endogenous
 compound
 angiostatin: EC, endogenous compound
 angiogenesis inhibitor: EC, endogenous compound
 unindexed drug
 unclassified drug

CAS REGISTRY NO.: (vasculotropin) 127464-60-2; (pigment epithelium derived
 factor) 197980-93-1; (combretastatin A4)
117048-59-6; (vasculotropin receptor) 301253-48-5;
 (rhodopsin) 60383-01-9, 9009-81-8; (growth hormone)
 36992-73-1, 37267-05-3, 66419-50-9, 9002-72-6; (somatomedin
 C) 67763-96-6; (angiopoietin 1) 186270-49-5; (angiopoietin
 2) 194368-66-6; (iodine 125) 14158-31-7, 22822-81-7;
 (nitric oxide synthase) 125978-95-2; (n(g) methylarginine)
 156706-47-7, **17035-90-4**; (proteinase inhibitor)
 37205-61-1; (plasminogen activator inhibitor 1)
 140208-23-7; (tissue inhibitor of metalloproteinase 1)
 140208-24-8; (angiostatin) 172642-30-7, 86090-08-6
 CHEMICAL NAME: Vitaxin

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 on STN DUPLICATE 4

ACCESSION NUMBER: 2002111730 EMBASE
 TITLE: Protease-mediated fragmentation of p-amidobenzyl ethers: A
 new strategy for the activation of anticancer prodrugs.
 AUTHOR: Toki B.E.; Cervený C.G.; Wahl A.F.; Senter P.D.
 CORPORATE SOURCE: P.D. Senter, Seattle Genetics, 21823 30th Drive SE,

SOURCE: Bothell, WA 98021, United States. psenter@seagen.com
Journal of Organic Chemistry, (22 Mar 2002) 67/6
(1866-1872).

Refs: 42

ISSN: 0022-3263 CODEN: JOCEAH

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer

030 Pharmacology

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT:

A new anticancer prodrug activation strategy based on the 1,6-elimination reaction of p-aminobenzyl ethers is described. Model studies were undertaken with the N-protected peptide benzyloxycarbonylvaline-citrulline (Z-val-cit), which was attached to the amino groups of p-aminobenzyl ether derivatives of 1-naphthol and N-acetylnorephedrine. The amide bond that formed was designed for hydrolysis by cathepsin B, a protease associated with rapidly growing and metastatic carcinomas. Upon treatment with the enzyme, the Z-val-cit-p-amidobenzyl ether of 1-naphthol (2) underwent peptide bond hydrolysis with the rapid release of 1-naphthol. The aliphatic Z-val-cit-p-amidobenzyl ether of N-acetylnorephedrine (5) also underwent amide bond hydrolysis, but without the ensuing elimination of N-acetylnorephedrine. On the basis of these results, the phenolic anticancer drugs etoposide (6) and combretastatin A-4 (7) were attached to the Z-val-cit-p-amidobenzyl alcohol through ether linkages, forming the peptide-drug derivatives 8 and 9, respectively. Both compounds were stable in aqueous buffers and serum and underwent ether fragmentation upon treatment with cathepsin B, resulting in the release of the parent drugs in chemically unmodified forms. The released drugs were 13-50 times more potent than were the prodrug precursors on a panel of cancer cell lines. In contrast, the corresponding carbonate derivative of combretastatin A-4 (13) was unstable in aqueous environments and was as cytotoxic as combretastatin A-4. This result extends the use of the self-immolative p-aminobenzyl group for the fragmentation of aromatic ethers and provides a new strategy for anticancer prodrug development.

CONTROLLED TERM: Medical Descriptors:

reaction analysis

molecular model

chemical bond

hydrolysis

aqueous solution

human

controlled study

human cell

article

Drug Descriptors:

*proteinase

*antineoplastic agent: AN, drug analysis

*antineoplastic agent: CM, drug comparison

*prodrug: AN, drug analysis

*prodrug: CM, drug comparison

*benzyloxycarbonylvaline citrulline 4 amidobenzyl 3' o

combretastatin A4: AN, drug analysis

*benzyloxycarbonylvaline citrulline 4 amidobenzyl 3' o

combretastatin A4: CM, drug comparison

*citrulline: AN, drug analysis

*citrulline: CM, drug comparison

*peptide: AN, drug analysis

*peptide: CM, drug comparison

1 naphthol

norephedrine: AN, drug analysis
 norephedrine: CM, drug comparison
 n acetylnorephedrine: AN, drug analysis
 n acetylnorephedrine: CM, drug comparison
 etoposide: AN, drug analysis
 etoposide: CM, drug comparison
 combretastatin A4: AN, drug analysis
 combretastatin A4: CM, drug comparison
 cytotoxic agent: AN, drug analysis
 cytotoxic agent: CM, drug comparison
 cathepsin B
 unclassified drug

CAS REGISTRY NO.: (proteinase) 9001-92-7; (citrulline) 372-75-8; (1
 naphthol) 90-15-3; (norephedrine) 700-65-2; (etoposide)
 33419-42-0; (combretastatin A4) 117048-59-6;
 (cathepsin B) 9047-22-7

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 on STN

ACCESSION NUMBER: 2004149963 EMBASE
 TITLE: Combretastatin A4 phosphate.
 AUTHOR: West C.M.L.; Price P.
 CORPORATE SOURCE: P. Price, Acad. Dept. of Radiation Oncology, Christie NHS
 Trust Hospital, Wilmslow Road, Manchester M20 4BX, United
 Kingdom. pat.price@man.ac.uk
 SOURCE: Anti-Cancer Drugs, (2004) 15/3 (179-187).
 Refs: 83
 ISSN: 0959-4973 CODEN: ANTDEV
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 014 Radiology
 016 Cancer
 030 Pharmacology
 037 Drug Literature Index
 038 Adverse Reactions Titles
 LANGUAGE: English
 SUMMARY LANGUAGE: English

ABSTRACT:
 Combretastatin A4 phosphate (CA4P) is a water-soluble prodrug of combretastatin
 A4 (CA4). The vascular targeting agent CA4 is a microtubule depolymerizing
 agent. The mechanism of action of the drug is thought to involve the binding of
 CA4 to tubulin leading to cytoskeletal and then morphological changes in
 endothelial cells. These changes increase vascular permeability and disrupt
 tumor blood flow. In experimental tumors, anti-vascular effects are seen within
 minutes of drug administration and rapidly lead to extensive ischemic necrosis
 in areas that are often resistant to conventional anti-cancer treatments.
 Following single-dose administration a viable tumor rim typically remains from
 which tumor regrowth occurs. When given in combination with therapies targeted
 at the proliferating viable rim, enhanced tumor responses are seen and in some
 cases cures. Results from the first clinical trials have shown that CA4P
 monotherapy is safe and reduces tumor blood flow. There has been some promising
 demonstration of efficacy. CA4P in combination with cisplatin is also safe.
 Functional imaging studies have been used to aid the selection of doses for
 phase II trials. Both dynamic contrast-enhanced magnetic resonance imaging
 (DCE-MRI) and positron emission tomography can measure the anti-vascular
 effects of CA4P in humans. This review describes the background to the
 development of CA4P, its proposed mechanism of action, the results from the
 first clinical trials with CA4P and the role of imaging techniques in its
 clinical development. .COPYRGHT. 2004 Lippincott Williams & Wilkins.

CONTROLLED TERM: Medical Descriptors:
 drug mechanism

tumor blood flow
drug safety
drug efficacy
nuclear magnetic resonance imaging
positron emission tomography
endothelium cell
blood vessel permeability
tumor vascularization
cell growth
polymerization
protein phosphorylation
actin polymerization
antineoplastic activity
hyperthermia
radioimmunotherapy
fatigue: SI, side effect
lung toxicity: SI, side effect
hot flush: SI, side effect
pruritus: SI, side effect
nausea: SI, side effect
vomiting: SI, side effect
headache: SI, side effect
abdominal cramp: SI, side effect
QT prolongation: DI, diagnosis
QT prolongation: SI, side effect
cardiotoxicity: SI, side effect
blood toxicity: SI, side effect
syncope: SI, side effect
motor neuropathy: SI, side effect
ataxia: SI, side effect
thyroid cancer: DI, diagnosis
thyroid cancer: DT, drug therapy
kidney cancer: DT, drug therapy
lung non small cell cancer: DT, drug therapy
intestine ischemia: SI, side effect
maximum tolerated dose
area under the curve
human
nonhuman
clinical trial
review
priority journal
Drug Descriptors:
*combretastatin A4 phosphate: AE, adverse drug reaction
*combretastatin A4 phosphate: CT, clinical trial
*combretastatin A4 phosphate: CB, drug combination
*combretastatin A4 phosphate: DO, drug dose
*combretastatin A4 phosphate: DT, drug therapy
*combretastatin A4 phosphate: PK, pharmacokinetics
*combretastatin A4 phosphate: PD, pharmacology
*combretastatin A4 phosphate: IV, intravenous drug
administration
 combretastatin A4: CT, clinical trial
 combretastatin A4: PR, pharmaceutics
 combretastatin A4: PD, pharmacology
tubulin: EC, endogenous compound
cisplatin: CB, drug combination
colchicine: EC, endogenous compound
mitoflaxone
tumor necrosis factor alpha
vincristine
vinblastine

antibody
 toxin
 5,6 dimethylxanthenone 4 acetic acid
 Vinca alkaloid
 actin: EC, endogenous compound
 myosin: EC, endogenous compound
 growth factor
 cytokine
 myosin light chain: EC, endogenous compound
 Rho kinase: EC, endogenous compound
 Rho guanosine triphosphatase
 nitric oxide synthase: EC, endogenous compound
 carboplatin: CB, drug combination
 doxorubicin: CB, drug combination
 cyclophosphamide: CB, drug combination
 fumagillol chloroacetylcarbamate: CB, drug combination
 fluorouracil: CB, drug combination
 iodine 125
 carcinoembryonic antibody: CB, drug combination
 gadolinium pentetate: IV, intravenous drug administration
nitric oxide synthase inhibitor

CAS REGISTRY NO.: (combretastatin A4 phosphate) 168555-66-6,
 222030-63-9; (combretastatin A4)
 117048-59-6; (cisplatin) 15663-27-1, 26035-31-4,
 96081-74-2; (colchicine) 64-86-8; (mitoflaxone) 87626-55-9;
 (vincristine) 57-22-7; (vinblastine) 865-21-4; (nitric
 oxide synthase) 125978-95-2; (carboplatin) 41575-94-4;
 (doxorubicin) 23214-92-8, 25316-40-9; (cyclophosphamide)
 50-18-0; (fumagillol chloroacetylcarbamate) 129298-91-5;
 (fluorouracil) 51-21-8; (iodine 125) 14158-31-7,
 22822-81-7; (gadolinium pentetate) 80529-93-7
 CHEMICAL NAME: Tnp 470

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ACCESSION NUMBER: 2002216312 EMBASE
 TITLE: Small-molecule, tubulin-binding compounds as vascular
 targeting agents.
 AUTHOR: Marx M.A.
 CORPORATE SOURCE: Dr. M.A. Marx, Pfizer Global Research/Development, Pfizer
 Corporation, Eastern Point Road, Groton, CT 06340, United
 States
 SOURCE: Expert Opinion on Therapeutic Patents, (2002) 12/6
 (769-776).
 Refs: 38
 ISSN: 1354-3776 CODEN: EOTPEG
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 016 Cancer
 030 Pharmacology
 037 Drug Literature Index
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ABSTRACT:

Vascular targeting or vascular damaging agents are directed toward established
 blood vessels, making them different from antiangiogenic agents, which inhibit
 one or more of the processes of neo-vascularisation. This emerging area of
 cancer drug discovery is currently being clinically tested and there is growing
 activity directed toward the identification of new antivascular agents. This
 review summarises key aspects of recent patents and patent applications
 referring to cancer chemotherapy and cancer drug discovery that involve the
 targeting or destruction of established vasculature. This review focuses on

applications that have been published between January 2000 and December 2001, with earlier, selected references included. Small molecule approaches, such as analogues of combretastatin A-4 (CA4) and colchicine, as well as other novel chemotypes, are the major focus of this review.

CONTROLLED TERM: Medical Descriptors:
protein binding
drug targeting
blood vessel
blood vessel injury
cancer chemotherapy
drug identification
patent
tumor vascularization
neovascularization (pathology)
drug mechanism
antineoplastic activity
drug structure
structure activity relation
dose response
nonhuman
mouse
controlled study
review
Drug Descriptors:
*combretastatin A4: AN, drug analysis
*combretastatin A4: DV, drug development
*combretastatin A4: PD, pharmacology
*colchicine: AN, drug analysis
*colchicine: DV, drug development
*colchicine: PD, pharmacology
tubulin: EC, endogenous compound
angiogenesis inhibitor
prodrug: AN, drug analysis
prodrug: PD, pharmacology
combretastatin A4 phosphate: AN, drug analysis
combretastatin A4 phosphate: PD, pharmacology
stilbene: AN, drug analysis
stilbene: PD, pharmacology
stilbene derivative: AN, drug analysis
stilbene derivative: PD, pharmacology
combretastatin
combretastatin A1: AN, drug analysis
combretastatin A1: DV, drug development
combretastatin A1: PD, pharmacology
combretastatin B1: AN, drug analysis
combretastatin B1: DV, drug development
combretastatin B1: PD, pharmacology
combretastatin derivative: CB, drug combination
combretastatin derivative: PD, pharmacology
nitric oxide synthase inhibitor: CB, drug combination
nitric oxide synthase inhibitor: PD, pharmacology
aminoguanidine: PD, pharmacology
carboxylic acid
phosphate
sulfate
carbonic acid
cisplatin: CB, drug combination
cisplatin: PD, pharmacology
hydroxyphenstatin: AN, drug analysis
hydroxyphenstatin: DV, drug development

hydroxyphenstatin: PD, pharmacology
 dioxostatin: AN, drug analysis
 dioxostatin: DV, drug development
 dioxostatin: PD, pharmacology
 colchicine derivative: AN, drug analysis
 colchicine derivative: DV, drug development
 colchicine derivative: PD, pharmacology
 n acetylcolchinol: AN, drug analysis
 n acetylcolchinol: CM, drug comparison
 n acetylcolchinol: DV, drug development
 n acetylcolchinol: PD, pharmacology
 zd 6126: AN, drug analysis
 zd 6126: CB, drug combination
 zd 6126: DV, drug development
 zd 6126: DO, drug dose
 zd 6126: PD, pharmacology
 paclitaxel: CB, drug combination
 nocodazole: AN, drug analysis
 nocodazole: PD, pharmacology
 nocodazole derivative: AN, drug analysis
 nocodazole derivative: DV, drug development
 nocodazole derivative: PD, pharmacology
 benzothiophene: PD, pharmacology
 polycyclic aromatic hydrocarbon derivative: PD,
 pharmacology
 unindexed drug
 unclassified drug

CAS REGISTRY NO.: (combretastatin A4) 117048-59-6; (colchicine)
 64-86-8; (stilbene) 588-59-0; (combretastatin) 82855-09-2,
 89064-44-8; (aminoguanidine) 1068-42-4, 2582-30-1,
 79-17-4; (phosphate) 14066-19-4, 14265-44-2;
 (sulfate) 14808-79-8; (carbonic acid) 3812-32-6, 463-79-6;
 (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2;
 (paclitaxel) 33069-62-4; (nocodazole) 31430-18-9;
 (benzothiophene) 95-15-8
 CHEMICAL NAME: (1) Zd 6126; (2) Zd 6126
 COMPANY NAME: (1) Astra Zeneca; (2) Angiogene; Oxigene

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ACCESSION NUMBER: 2002182701 EMBASE
 TITLE: Angiogenesis: From the molecular mechanisms to the
 development of new drugs.
 AUTHOR: Morbidelli L.; Donnini S.; D'Amore V.; Ziche M.
 CORPORATE SOURCE: L. Morbidelli, Istituto di Scienze Farmacologiche,
 Universita di Siena, Siena, Italy
 SOURCE: Acta Medica Romana, (2001) 39/2 (238-246).
 Refs: 24
 ISSN: 0001-6098 CODEN: AMROBA
 COUNTRY: Italy
 DOCUMENT TYPE: Journal; Conference Article
 FILE SEGMENT: 005 General Pathology and Pathological Anatomy
 030 Pharmacology
 037 Drug Literature Index
 LANGUAGE: English
 SUMMARY LANGUAGE: English; Italian
 ABSTRACT:

The steps required for new vessel growth are biologically complex and require
 coordinate regulation of contributing components, including modifications of
 cell-cell interactions, proliferation and migration of endothelial cells and
 matrix degradation. The observation that in vivo angiogenesis is accompanied by
 vasodilation, that many angiogenesis effectors possess vasodilating properties

and that tumor vasculature is in a persistent state of vasodilation, support the existence of a molecular/biochemical link between vasodilation and angiogenesis. Several pieces of evidence converge in the indication of a role for nitric oxide (NO), the factor responsible for vasodilation, in physiological and pathological angiogenesis. Data originated in different labs indicate that NO can act both as an "actor" of angiogenesis and as a "director of angiogenesis", both functions being equally expressed during physiological and pathological processes. NO significantly contributes to the prosurvival/proangiogenic program of capillary endothelium by triggering and transducing cell growth and differentiation via endothelial-constitutive NO synthase (ec-NOS) activation, cyclic GMP (cGMP) elevation, mitogen activated kinase (MAPK) activation and fibroblast growth factor-2 (FGF-2) expression. Re-establishment of a balanced NO production in the cardiovascular system results in a reduction of cell damage during inflammatory and vascular diseases. Elevation of NOS activity in correlation with angiogenesis and tumor progression has been extensively reported in experimental and human tumors. Tumor expansion and edema formation are sensitive to NOS inhibition. On this basis, the nitric oxide pathway appears to be a promising target for consideration in pro- and antiangiogenic therapeutic strategies. The use of NOS inhibitors seems appropriate to reduce edema, block angiogenesis and facilitate antitumor drug delivery.

CONTROLLED TERM: Medical Descriptors:

- *angiogenesis
- *neovascularization (pathology): ET, etiology
- drug screening
- regulatory mechanism
- cell interaction
- cell proliferation
- cell migration
- endothelium cell
- extracellular matrix
- in vivo study
- vasodilatation
- tumor vascularization
- pathogenesis
- capillary endothelium
- signal transduction
- cell growth
- cell differentiation
- enzyme activation
- cell level
- protein expression
- mediator release
- inflammation
- vascular disease
- enzyme activity
- correlation analysis
- tumor growth
- edema: ET, etiology
- enzyme inhibition
- drug targeting
- drug mechanism
- drug delivery system
- human
- nonhuman
- conference paper

Drug Descriptors:

- *angiogenesis inhibitor: PD, pharmacology
- nitric oxide: EC, endogenous compound**
- nitric oxide synthase: EC, endogenous compound
- cyclic GMP: EC, endogenous compound

mitogen activated protein kinase: EC, endogenous compound
 fibroblast growth factor 2: EC, endogenous compound
 batimastat: PD, pharmacology
 marimastat: PD, pharmacology
 prinomastat: PD, pharmacology
 ae 941: PD, pharmacology
 amiloride: PD, pharmacology
 minocycline: PD, pharmacology
 monoclonal antibody lm 609: PD, pharmacology
 benzodiazepine derivative: PD, pharmacology
 endostatin: PD, pharmacology
 alpha interferon: PD, pharmacology
 gamma interferon: PD, pharmacology
 interleukin 12: PD, pharmacology
nitric oxide synthase inhibitor: PD, pharmacology
 thrombospondin 1: PD, pharmacology
 fumagillol chloroacetylcarbamate: PD, pharmacology
combretastatin A4: PD, pharmacology
 thalidomide: PD, pharmacology
 roquinimex: PD, pharmacology
 thrombocyte factor 4: PD, pharmacology
 suramin: PD, pharmacology
 distamycin A: PD, pharmacology
 protamine: PD, pharmacology
 acetylsalicylic acid: PD, pharmacology
 unindexed drug

AS REGISTRY NO.:

(nitric oxide) 10102-43-9; (nitric oxide synthase)
 125978-95-2; (cyclic GMP) 7665-99-8; (mitogen activated
 protein kinase) 142243-02-5; (batimastat) 130370-60-4,
 130464-84-5; (marimastat) 154039-60-8; (prinomastat)
 192329-42-3, 195008-93-6; (amiloride) 2016-88-8, 2609-46-3;
 (minocycline) 10118-90-8, 11006-27-2, 13614-98-7;
 (endostatin) 187888-07-9; (gamma interferon) 82115-62-6;
 (interleukin 12) 138415-13-1; (thrombospondin 1)
 343987-56-4; (fumagillol chloroacetylcarbamate)
 129298-91-5; (combretastatin A4) **117048-59-6**;
 (thalidomide) 50-35-1; (roquinimex) 84088-42-6;
 (thrombocyte factor 4) 37270-94-3, 69670-74-2; (suramin)
 129-46-4, 145-63-1; (distamycin A) 13696-04-3, 39389-47-4,
 636-47-5; (protamine) 11061-43-1, 9007-31-2, 9012-00-4;
 (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4,
 53664-49-6, 63781-77-1

CHEMICAL NAME:

Ag 3340; Lm 609; Vitaxin; Tnp 470; Aspirin

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on STN

ACCESSION NUMBER:

1998235577 EMBASE

TITLE:

Modification of tumor blood flow: Current status and future
 directions.

AUTHOR:

Chaplin D.J.; Hill S.A.; Bell K.M.; Tozer G.M.

CORPORATE SOURCE:

D.J. Chaplin, Tumour Microcirculation Group, Gray Lab.
 Cancer Research Trust, Mount Vernon Hospital, Northwood,
 Middlesex HA6 2JR, United Kingdom

SOURCE:

Seminars in Radiation Oncology, (1998) 8/3 (151-163).
 Refs: 122

ISSN: 1053-4296 CODEN: SRONEO

COUNTRY:

United States

DOCUMENT TYPE:

Journal; General Review

FILE SEGMENT:

005 General Pathology and Pathological Anatomy
 016 Cancer
 030 Pharmacology
 037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:

Suboptimal drug distribution and hypoxia, which can contribute to treatment failure, are a direct consequence of the spatial and temporal heterogeneity in perfusion that occurs in solid tumors. Therefore, improvements in tumor blood flow have wide-ranging therapeutic importance. Paradoxically, controlled decreases in tumor blood flow can also be exploited and, if permanent, induce extensive tumor cell death on their own. We review the current knowledge of the factors controlling tumor blood flow with emphasis on the roles of the endogenous vasodilator nitric oxide and the endogenous vasoconstrictor endothelin-1. The potential importance and application of approaches that irreversibly damage vascular function, so-called vascular targeting, are also discussed. Emphasis is given to the drug-based approaches to vascular targeting that are now entering clinical evaluation. There is no doubt that increased understanding of the processes that determine blood flow in tumors, coupled with the availability of techniques to monitor blood flow noninvasively in the clinic, will enable strategies for selectively modifying tumor blood flow to be transferred from the laboratory to the clinical setting.

CONTROLLED TERM: Medical Descriptors:
*tumor blood flow
*tumor vascularization
*antineoplastic activity
drug distribution
hypoxia: ET, etiology
treatment failure
angiogenesis
metastasis potential: CO, complication
drug delivery system
perfusion pressure
vascular resistance
vasoconstriction
vasodilatation
hyperthermic therapy
human
nonhuman
review
priority journal
Drug Descriptors:
*nitric oxide: EC, endogenous compound
*endothelin 1: EC, endogenous compound
*antineoplastic agent: PK, pharmacokinetics
*antineoplastic agent: PD, pharmacology
*nitric oxide synthase: EC, endogenous compound
*angiogenesis inhibitor: PD, pharmacology
n(g) nitroarginine methyl ester
n(g) methylarginine
n(g) nitroarginine
diethylamine
endothelin receptor: EC, endogenous compound
oxygen
carbon dioxide
angiotensin: PD, pharmacology
hydralazine: DO, drug dose
hydralazine: PD, pharmacology
nicotinamide: PD, pharmacology
mitoflaxone: PD, pharmacology
dimethylxanthone acetic acid: PD, pharmacology
colchicine: PD, pharmacology
combretastatin a4: DV, drug development
combretastatin a4: PD, pharmacology

tumor necrosis factor alpha: PD, pharmacology
 unclassified drug
 CAS REGISTRY NO.: (nitric oxide) 10102-43-9; (nitric oxide synthase)
 125978-95-2; (n(g) nitroarginine methyl ester) 50903-99-6;
 (n(g) methylarginine) **17035-90-4**; (n(g)
 nitroarginine) **2149-70-4**; (diethylamine)
 109-89-7, 660-68-4; (oxygen) 7782-44-7; (carbon dioxide)
 124-38-9, 58561-67-4; (angiotensin) 11128-99-7, 1407-47-2;
 (hydralazine) 304-20-1, 86-54-4; (nicotinamide) 11032-50-1,
 98-92-0; (mitoflaxone) 87626-55-9; (colchicine) 64-86-8;
 (combretastatin a4) **117048-59-6**

89 ANSWER 20 OF 27 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
 DUPLICATE
 ACCESSION NUMBER: 2002:35386461 BIOTECHNO
 TITLE: Gephyrin **interacts** with dynein light chains
 1 and 2, components of motor protein complexes
 AUTHOR: Fuhrmann J.C.; Kins S.; Rostaing P.; El Far O.; Kirsch
 J.; Sheng M.; Triller A.; Betz H.; Kneussel M.
 CORPORATE SOURCE: H. Betz, Max-Planck-Inst. for Brain Research,
 Department of Neurochemistry, Deutschordenstrasse 46,
 D-60528 Frankfurt/Main, Germany.
 SOURCE: E-mail: neurochemie@mpih-frankfurt.mpg.de
 Journal of Neuroscience, (01 JUL 2002), 22/13
 (5393-5402), 53 reference(s)
 CODEN: JNRSDS ISSN: 0270-6474
 DOCUMENT TYPE: Journal; Article
 COUNTRY: United States
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ABSTRACT: The clustering of glycine receptors and major subtypes
 of GABA.sub.A receptors at inhibitory synapses is
 mediated by the **tubulin-binding**
 protein gephyrin. In an attempt to identify additional
 components of inhibitory postsynaptic specializations,
 we performed a yeast two-hybrid screen using gephyrin
 as bait. Multiple positive clones encoded either the
 dynein light chain-1 (Dlc-1), also known as dynein LC8
 and protein **inhibitor** of neuronal
nitric oxide synthase, or its
 homolog Dlc-2. Dlc-1 protein bound efficiently to
 gephyrin in in vitro binding assays and colocalized
 with gephyrin during coexpression in HEK293 cells. The
 binding site for Dlc was mapped to a fragment of 63
 amino acids within the central linker domain of
 gephyrin. In hippocampal neurons, endogenous Dlc
 protein was enriched at synaptic sites identified by
 synaptophysin and gephyrin immunostaining.
 Immunoelectron microscopy in spinal cord sections
 revealed Dlc immunoreactivity at the edges of
 postsynaptic differentiations, in close contact with
 cytoskeletal structures and at the periphery of the
 Golgi apparatus. Because Dlc-1 and Dlc-2 have been
 described as stoichiometric components of cytoplasmic
 dynein and myosin-Va complexes, our results suggest
 that motor proteins are involved in the subcellular
 localization of gephyrin.
 CONTROLLED TERM: *protein binding; *nucleotide sequence; *gephyrin;
 *dynein adenosine triphosphatase; *dynein light chain
 1; *dynein light chain 2; complex formation;
 postsynaptic inhibition; two hybrid system; binding
 assay; protein protein **interaction**; protein

localization; protein expression; cell line; binding site; amino acid sequence; protein domain; hippocampus; immunohistochemistry; immunoelectron microscopy; spinal cord; cytoskeleton; immunoreactivity; Golgi complex; stoichiometry; human; human cell; article; priority journal; protein inhibitor; **nitric oxide** synthase

CAS REGISTRY NUMBER: (gephyrin) 147570-97-6
GENE NUMBER: GENBANK AY034383 submitted number

L89 ANSWER 21 OF 27 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER: 1992:22077141 BIOTECHNO
TITLE: The 93 kDa protein gephyrin and tubulin associated with the inhibitory glycine receptor are phosphorylated by an endogenous protein kinase
AUTHOR: Langosch D.; Hoch W.; Betz H.
CORPORATE SOURCE: Abteilung Neurochemie, Max-Planck-Institut, fur Hirnforschung, Deutschordenstrasse 46, D-6000 Frankfurt 71, Germany.
SOURCE: FEBS Letters, (1992), 298/2-3 (113-117)
CODEN: FEBLAL ISSN: 0014-5793
DOCUMENT TYPE: Journal; Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT: The 93 kDa protein gephyrin is a **tubulin binding** peripheral membrane protein that is associated with the inhibitory glycine receptor and has been implicated in its anchoring at central synapses. Here, we demonstrate that gephyrin as well as co-purifying tubulin are phosphorylated by a kinase activity which is endogenous to highly purified glycine receptor preparations. This kinase phosphorylates serine and threonine residues and utilizes ATP, but not GTP, as phosphate donor. Its activity is not affected by various activators and/or inhibitors of cyclic nucleotide-dependent kinases, calcium/calmodulin-dependent kinases, or protein kinase C. A five-fold stimulation of kinase activity was, however, observed in the presence of poly-**lysine**. Phosphorylation of gephyrin and/or tubulin might regulate receptor/cytoskeleton **interactions** at postsynaptic membrane specializations.

CONTROLLED TERM: *glycine receptor; *membrane protein; *protein kinase; *tubulin; *protein phosphorylation; gephyrin; article; priority journal
CAS REGISTRY NUMBER: (protein kinase) 9026-43-1; (gephyrin) 147570-97-6

L89 ANSWER 22 OF 27 TOXCENTER COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:69138 TOXCENTER
COPYRIGHT: Copyright 2004 ACS
TITLE: Protease mediated fragmentation of p-amidobenzylethers: A new strategy for the activation of anticancer prodrugs
AUTHOR(S): Toki, Brian E.; Senter, Peter
CORPORATE SOURCE: Seattle Genetics, Bothell, WA, 98021, USA.
SOURCE: Abstracts of Papers, 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002, (2002) pp. MEDI-197.
CODEN: 69CKQP.
COUNTRY: UNITED STATES

DOCUMENT TYPE: Conference
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2002:190316
LANGUAGE: English
ENTRY DATE: Entered STN: 20020319
Last Updated on STN: 20020319

ABSTRACT:

A new anticancer prodrug activation strategy based on the 1,6-elimination reaction of p-aminobenzyl ethers is described. Model studies were undertaken with the peptide Z-valine-citrulline (Z-val-cit), which was attached to the amino groups of p-aminobenzyl ether derivs. of 1-naphthol and N-acetylnorephedrine. The amide bond formed was designed for hydrolysis by cathepsin B, a protease assocd. with rapidly growing and metastatic carcinomas. Upon treatment with the enzyme, the Z-val-cit-p-amidobenzyl ether of 1-naphthol underwent peptide bond hydrolysis with rapid release of 1-naphthol. The aliph. Z-val-cit-p-amidobenzyl ether of N-acetylnorephedrine also underwent amide bond hydrolysis, but without the ensuing elimination of N-acetylnorephedrine. Based on these results, the phenolic anticancer **drugs**, etoposide and *****combretastatin*** A-4** were attached to the Z-val-cit-p-amidobenzyl alc. through ether linkages. Both compds. were stable in aq. buffers and serum, and underwent ether fragmentation upon treatment with cathepsin B, resulting in the release of the parent drugs in chem. unmodified form. The released drugs were 13-22 times more potent than the prodrug precursors on a panel of cancer cell lines. In contrast, the corresponding carbonate deriv. of **combretastatin A-4** was unstable in aq. environments and was as cytotoxic as **combretastatin ***A*** -4**. This extends the use of the self-immolative p-aminobenzyl group for the fragmentation of arom. ethers and provides a new strategy for anticancer prodrug development.

L89 ANSWER 23 OF 27 TOXCENTER COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:34147 TOXCENTER
DOCUMENT NUMBER: PubMed ID: 9190213
TITLE: Functional **interactions** between the proline-rich and repeat regions of tau enhance microtubule binding and assembly
AUTHOR(S): Goode B L; Denis P E; Panda D; Radeke M J; Miller H P; Wilson L; Feinstein S C
CORPORATE SOURCE: Department of Molecular, Cellular, and Developmental Biology, University of California, Santa Barbara 93106, USA
CONTRACT NUMBER: NS13560 (NINDS)
NS35010 (NINDS)
SOURCE: Molecular biology of the cell, (1997 Feb) 8 (2) 353-65.
Journal Code: 9201390. ISSN: 1059-1524.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 97206133
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

ABSTRACT:

Tau is a neuronal microtubule-associated protein that promotes microtubule assembly, stability, and bundling in axons. Two distinct regions of tau are important for the tau-microtubule **interaction**, a relatively well-characterized "repeat region" in the carboxyl terminus (containing either three or four imperfect 18-amino acid repeats separated by 13- or 14-amino acid long inter-repeats) and a more centrally located, relatively poorly characterized proline-rich region. By using amino-terminal truncation analyses of tau, we have localized the microtubule binding activity of the proline-rich region to Lys215-Asn246 and identified a small sequence within this region,

215KKVAVVR221, that exerts a strong influence on microtubule binding and assembly in both three- and four-repeat tau isoforms. Site-directed mutagenesis experiments indicate that these capabilities are derived largely from Lys215/Lys216 and Arg221. In marked contrast to synthetic peptides corresponding to the repeat region, peptides corresponding to Lys215-Asn246 and Lys215-Thr222 alone possess little or no ability to promote microtubule assembly, and the peptide Lys215-Thr222 does not effectively suppress in vitro microtubule dynamics. However, combining the proline-rich region sequences (Lys215-Asn246) with their adjacent repeat region sequences within a single peptide (Lys215-Lys272) enhances microtubule assembly by 10-fold, suggesting intramolecular **interactions** between the proline-rich and repeat regions. Structural complexity in this region of tau also is suggested by sequential amino-terminal deletions through the proline-rich and repeat regions, which reveal an unusual pattern of loss and gain of function. Thus, these data lead to a model in which efficient microtubule binding and assembly activities by tau require intramolecular **interactions** between its repeat and proline-rich regions. This model, invoking structural complexity for the microtubule-bound conformation of tau, is fundamentally different from previous models of tau structure and function, which viewed tau as a simple linear array of independently acting **tubulin-binding** sites.

CONTROLLED TERM: Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Amino Acid Sequence
Asparagine
Binding Sites
Lysine
*Microtubules: ME, metabolism
Microtubules: PH, physiology
Molecular Sequence Data
Peptides: CS, chemical synthesis
Peptides: CH, chemistry
Peptides: ME, metabolism
*Proline: ME, metabolism
Structure-Activity Relationship
tau Proteins: CH, chemistry
*tau Proteins: ME, metabolism
REGISTRY NUMBER: 147-85-3 (Proline)
56-87-1 (Lysine)
7006-34-0 (Asparagine)
CHEMICAL NAME: 0 (Peptides); 0 (proline-rich polypeptide); 0 (tau Proteins)

L89 ANSWER 24 OF 27 TOXCENTER COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:200494 TOXCENTER
COPYRIGHT: Copyright 2004 ACS
DOCUMENT NUMBER: CA12317225061D
TITLE: .tau. Protein from Alzheimer's disease patients is glycosylated at its **tubulin-binding** domain
AUTHOR(S): Ledesma, M. Dolores; Bonay, Pedro; Avila, Jesus
CORPORATE SOURCE: Centro Biologia Molecular "Severo Ochoa", Univ. Autonoma Madrid, Madrid, Spain.
SOURCE: Journal of Neurochemistry, (1995) Vol. 65, No. 4, pp. 1658-64.
CODEN: JONRA9. ISSN: 0022-3042.
COUNTRY: SPAIN
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1995:817710
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20030617
ABSTRACT:

Glycated residues of .tau. protein from paired helical filaments isolated from the brains of Alzheimer's disease patients were localized by doing a proteolytic cleavage of the protein, fractionation of the resulting peptides, and identification of those peptide using specific antibodies. The most suitable residues for glycation, lysines, present at the **tubulin-***binding***** motif of .tau. protein, seem to be preferentially modified compared with those lysines present at other regions. Among these modified lysines, those located in the sequence comprising residues 318-336 (in the largest human .tau. isoform) were found to be glycated, as detd. by the reaction with an antibody that recognizes a glycated peptide contg. this sequence. Because those lysines are present in a **tubulin-***binding***** motif of .tau. protein, its modification could result in a decrease in the **interaction** of .tau. with tubulin.

CLASSIFICATION CODE: 14-10

SUPPLEMENTARY TERMS: Miscellaneous Descriptors

tau protein glycation tubulin domain Alzheimer

REGISTRY NUMBER: 56-87-1 (**Lysine**)

L89 ANSWER 25 OF 27 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2003-239101 [23] WPIDS

DOC. NO. CPI: C2003-061206

TITLE: Novel compound useful for treating cancer, tumors and inflammatory diseases, cleavable by CD10, and has therapeutic agent capable of entering target cell, oligopeptide, stabilizing group and linker group.

DERWENT CLASS: A96 B04 D16

INVENTOR(S): BEBBINGTON, C R; CARDARELLI, P M; GANGWAR, S; NIEDER, M H; PAN, C; PICKFORD, L B

PATENT ASSIGNEE(S): (MEDA-N) MEDAREX INC; (BEBB-I) BEBBINGTON C R; (CARD-I) CARDARELLI P M; (GANG-I) GANGWAR S; (NIED-I) NIEDER M H; (PANC-I) PAN C; (PICK-I) PICKFORD L B

COUNTRY COUNT: 101

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2002100353	A2	20021219	(200323)*	EN	167	A61K000-00	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ							
NL OA PT SD SE SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT							
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM							
ZW							
EP 1404356	A2	20040407	(200425)	EN		A61K038-06	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT							
RO SE SI TR							
US 2004087497	A1	20040506	(200430)			A61K038-17	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002100353	A2	WO 2002-US21135	20020610
EP 1404356	A2	EP 2002-746852	20020611
		WO 2002-US21135	20020611
US 2004087497	A1 Provisional	US 2001-297596P	20010611
		US 2002-167627	20020611

FILING DETAILS:

PATENT NO	KIND	PATENT NO

EP 1404356 A2 Based on WO 2002100353

PRIORITY APPLN. INFO: US 2001-297596P 20010611; US
2002-167627 20020611

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K038-06; A61K038-17
SECONDARY: A61K031-337; A61K031-704; A61K031-7048; A61K031-7072;
A61K031-7076; A61K038-07; A61K038-08; A61K038-13;
C07K001-16; C07K005-08; C07K005-10; C07K007-06;
C12Q001-37

BASIC ABSTRACT:

WO2002100353 A UPAB: 20030407

NOVELTY - A compound (I) comprising therapeutic agent (TA) capable of entering target cell, oligopeptide (OP), stabilizing group (SG) and optionally, linker group (LG), and cleavable by CD10, is new.

DETAILED DESCRIPTION - OP is directly linked to SG at first attachment site of OP and OP is directly linked to TA or indirectly linked through LG to TA at second attachment site of OP, and SG hinders cleavage of (I) by enzymes present in blood.

(I) comprises TA capable of entering a target cell, OP of the formula (AA)n-AA(P2)-AA(P1)-AA(P1')-(AA)m, where n and m are integers, AA(P2), AA(P1) and AA(P1') represents any amino acid, and each AA independently represents an amino acid, SG, and optionally, LG, where (I) is cleavable by CD10, OP is directly linked to SG at a first attachment site of OP and OP is directly linked to TA or indirectly linked through LG to TA at a second attachment site of OP, SG hinders cleavage of (I) by enzymes present in whole blood, if OP is Leu-Ala-Leu, then SG is not succinyl or beta Ala or TA is not one of doxorubicin and daunorubicin, if OP is beta Ala-Leu-Ala-Leu, then SG is not succinyl or TA is not one of doxorubicin and daunorubicin, if OP is beta Ala-Leu-Ala-Leu, then SG is not glutaryl or TA is not doxorubicin, and (I) is not chosen from Succ-Ala-Leu-Ala-Leu-Dnr, pGlu-Ala-Leu-Ala-Leu-Dox, D-Ala-Leu-Ala-Leu-Dnr, D-Leu-Ala-Leu-Ala-Leu-Dnr, D-Leu-D-Ala-Leu-Ala-Leu-Dnr, Acetyl-His-Ser-Ser-Lys-Leu-Gln-Dox, Morpholinocarbonyl-His-Ser-Ser-Lys-Leu-Gln-Leu-Dox, N-(2-hydroxypropyl)methacrylamide-Gly-Phe-Leu-Gly-Dox, N-glutaryl-(4-hydroxypropyl)-Ala-Ser-Cyclohexylglycine-Gln-Ser-Leu-Dox, N-Cbz-Gly-Phe-Ala-Leu-Dox and N-Cbz-Gly-Phe-Ala-Leu-PABC-Dox.

INDEPENDENT CLAIMS are also included for:

- (1) a conjugate (II) comprising OP which is cleavable by CD10 or thermolysin-like enzyme;
- (2) a pharmaceutical composition (III) comprising (I) and a carrier;
- (3) production (M) of (I);
- (4) a prodrug produced by (M);
- (5) screening to identify OP useful for designing a prodrug, by providing (I), and testing if OP is cleavable by CD10, where cleavability by CD10 is indicative of OP as a candidate for designing a prodrug; and
- (6) an article of manufacture for diagnosis or assay comprising (I) which has a marker, OP, SG, and optionally LG not cleavable by CD10, and a reagent useful in the detection of the marker.

ACTIVITY - Cytostatic; Antiinflammatory; Anti-tumor.

The effect of Suc- beta Ala-Ile-Ala-Leu-Dox therapeutic agent on the survival of mice and on growth of the tumors in a mouse xenograft model was evaluated. Groups of ten nude mice, were subcutaneously implanted with chunks of doxorubicin-resistant colorectal carcinoma LS174t, and were allowed to grow to approximately 50 mg. They were treated intravenously with 0, 53 or 68 mg/kg of Suc- beta Ala-Ile-Ala-Leu-Dox (equivalent to 0, 30 or 38 mg/kg doxorubicin) at five day intervals for a total of five identical doses. Tumors and body weights were measured twice weekly for up to 60 days. Both doses were efficacious in reducing the growth of tumors compared with vehicle control animals. There were 4 and 2 long-term survivors in the low and high dose groups, respectively, compared with 0

in the vehicle control group. The Mean Day of Survival (MDS) in animals whose tumors reached 1.5 g prior to day 60 was significantly better in the low (29.7 days) and high (23.4 day) dose groups than in the vehicle control group (18.2 days). Thus, Suc- beta Ala-Ile-Ala-Leu-Dox was efficacious in this aggressive human tumor model, in which doxorubicin alone at its tolerated dose (3 mg/kg), under this dosing regimen, was ineffective.

MECHANISM OF ACTION - Inhibitor of tumor growth.

USE - (I) is useful for manufacturing a medicament for treating a disorder having CD10-associated target cells, such as cancer (e.g. prostate cancer, B-cell lymphoblastic leukemia, T-cell lymphoblastic leukemia, lymphoma, including B-cell lymphoma and non-Hodgkins' lymphoma, follicular lymphoma, Burkitt lymphoma, melanoma, ocular melanoma, cutaneous melanoma, colon adenocarcinomas, hepatocellular carcinomas, renal cell carcinoma, ovarian carcinoma, prostate adenocarcinoma, liver carcinoma, transitional cell carcinoma, pancreatic adenocarcinoma, lung carcinoma, breast carcinoma and colon carcinoma), neoplastic diseases, tumors, inflammatory diseases, and infectious diseases. The method involves detecting CD10 associated with a target cell, and administering (I) to the patient. The detecting step involves obtaining a sample of tissue, combining the sample with a CD10-specific antibody, and determining binding of the CD-10 specific antibody to the sample. (I) is also useful for decreasing toxicity of TA which is intended for administration to a patient, by covalently forming a prodrug by linking OP cleavable by CD10 to SG at a first attachment site of OP and directly or indirectly linking TA at a second attachment site of OP, so that the prodrug is cleavable by CD10. The prodrug allows for administration of an increased dosage of TA in prodrug form to the patient relative to the dosage of TA in unconjugated form (all claimed). (I) is useful for diagnosing CD10 positive tumors.

ADVANTAGE - (I) has high specificity of action, reduced toxicity, improved stability in the serum and blood, improved therapeutic index, favorable pharmacokinetics, and does not move into target cells, or moves only minimally until activated by CD10.

DESCRIPTION OF DRAWING(S) - The figure is a schematic diagram showing cleavage of a prodrug in the extracellular vicinity of the target cell and within the target cell.

Dwg.2/35

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; GI
 MANUAL CODES: CPI: A12-V01; B04-B04D; B04-C01; B04-F01; B04-L01;
 B04-N04; B11-C07; B12-K04A; B12-K04E; B14-A01;
 B14-A02; B14-C03; B14-H01; D05-A02; D05-C11;
 D05-H09; D05-H17A6

L89 ANSWER 26 OF 27 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
 ACCESSION NUMBER: 1998:910300 SCISEARCH
 THE GENUINE ARTICLE: 141VC
 TITLE: Modification of tau to an Alzheimer's type protein
 interferes with its **interaction** with
 microtubules
 AUTHOR: Gonzalez C; Farias G; Maccioni R B (Reprint)
 CORPORATE SOURCE: UNIV CHILE, FAC SCI, MOL & CELLULAR BIOL LAB, CASILLA
 70111, SANTIAGO 7, CHILE (Reprint); UNIV CHILE, FAC SCI,
 MOL & CELLULAR BIOL LAB, SANTIAGO 7, CHILE; INT CTR CANC &
 DEV BIOL, SANTIAGO 7, CHILE
 COUNTRY OF AUTHOR: CHILE
 SOURCE: CELLULAR AND MOLECULAR BIOLOGY, (NOV 1998) Vol. 44, No. 7,
 pp. 1117-1127.
 Publisher: CELLULAR & MOLECULAR BIOLOGY, PROF R WEGMANN
 RESIDENCE HAUSSMANN 1 AVENUE DU PAVE NEUF, 93160
 NOISY-LE-GRAND, FRANCE.

ISSN: 0145-5680.

DOCUMENT TYPE: Article; Journal
 FILE SEGMENT: LIFE
 LANGUAGE: English
 REFERENCE COUNT: 45
 ABSTRACT:

The microtubule associated protein tau is the main structural component of paired helical filaments (PHFs), aberrant polymers found intracellularly in neurons of brains with the Alzheimers disease. Glycation is one of the posttranslational modifications that has been found in tau from PHFs, but not in normal brain tau. Studies were carried out with purified tau protein subjected to chemical modifications, in order to further investigate the mechanisms of tau self-association into PHFs. Tau was subjected to modifications affecting reactive lysyl residues, e.g., carbamoylation with potassium cyanate and glycation reaction with glucose. The effects of these modifications to produce functional alterations in tau capacity to bind brain tubulin and to induce microtubule assembly were investigated. Chemically-modified tau and tau of Alzheimer's type exhibited a similar microtubule **interaction** behavior as analysed by overlay assays, but those were different than normal tau controls. On the other hand, studies of the microtubule assembly kinetics indicated that the reported tau modifications resulted in a loss of its capacity to promote microtubule assembly from purified tubulin preparations. The data on the differences in the electrophoretic profiles, Western blots and the overlay patterns, along with those on the microtubule polymerisation of normal brain tau as compared with both modified and Alzheimer's tau, suggest changes in the functional behavior of this protein as a result of its structural modifications. These studies were complemented with an immunogold analysis at the electron microscope level, which indicated that the modified tau did not incorporate into assembled microtubules. These findings, combined with the results on tau chemical modifications suggest that the reactive **lysine** residues within functional domains on tau, e.g., those of the repetitive binding motifs, were affected by these modifications. Furthermore, these observations provide new clues to understand the anomalous **interactions** of tau in Alzheimer's disease.

CATEGORY: CELL BIOLOGY; BIOCHEMISTRY & MOLECULAR BIOLOGY
 SUPPLEMENTARY TERM: tau glycation; **tubulin binding**;
 microtubules; Alzheimer's disease
 SUPPL. TERM PLUS: PAIRED HELICAL FILAMENTS; CHEMICALLY-MODIFIED-TAU;
 SYNTHETIC PEPTIDES; REGULATORY DOMAIN; IMMUNOLOGICAL
 CHARACTERIZATION; NEUROFIBRILLARY DEGENERATION; ABNORMAL
 PHOSPHORYLATION; DISEASE; TUBULIN; BINDING

REFERENCE(S):

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
=====	=====	=====	=====	=====
ALONSO A D	1997	94	298	P NATL ACAD SCI USA
BANCHER C	1989	477	90	BRAIN RES
BIERNAT J	1993	11	153	NEURON
BINDER L I	1985	101	1371	J CELL BIOL
BUSCIGLIO J	1995	14	879	NEURON
BUSCIGLIO J	1993	90	2092	P NATL ACAD SCI USA
CAMBIAZO V	1995	64	1288	J NEUROCHEM
CAPUTO C B	1992	13	267	NEUROBIOL AGING
CLEVELAND D W	1990	60	701	CELL
CROSS D	1996	229	378	EXP CELL RES
ENNULAT D J	1989	264	5327	J BIOL CHEM
FARIAS G	1997	168	59	MOL CELL BIOCHEM
FARIAS G A	1993	13	173	CELL MOL NEUROBIOL
FARIAS G A	1992	112	81	MOL CELL BIOCHEM
FLAMENT S	1990	516	15	BRAIN RES

GOEDERT M	1988	85	4051	P NATL ACAD SCI USA
GREENBERG S G	1990	87	5827	P NATL ACAD SCI USA
GRUNDKEIQBAL I	1986	83	4913	P NATL ACAD SCI USA
HERZOG W	1978	92	1	EUR J BIOCHEM
IMAHORI K	1997	121	179	J BIOCHEM-TOKYO
IQBAL K	1989	248	87	FEBS LETT
IQBAL K	1986	2	421	LANCET
LAEMMLI U K	1970	227	680	NATURE
LEDESMA M D	1994	269	21614	J BIOL CHEM
LEE G	1988	239	285	SCIENCE
LEE V M Y	1991	251	675	SCIENCE
LINDWALL G	1984	259	5301	J BIOL CHEM
LIU W K	1991	266	21723	J BIOL CHEM
LOWRY O H	1951	193	265	J BIOL CHEM
MACCIONI R B	1989	275	568	ARCH BIOCHEM BIOPHYS
MACCIONI R B	1995	20	34	CIENCIA HOJE
MACCIONI R B	1988	7	1957	EMBO J
MACCIONI R B	1986			MOL CYTOLOGY MICROTU
MACCIONI R B	1996	75	835	PHYSIOL REV
MACCIONI R B	1992		153	PROGR CELL BIOL
MELLADO W	1982	203	675	BIOCHEM J
NACHARAJU P	1997	69	1709	J NEUROCHEM
OLTERS DORF T	1990	265	4465	J BIOL CHEM
RIVAS C I	1988	85	6092	P NATL ACAD SCI USA
RIVASBERRIOS A	1990	1040	382	BIOCHIM BIOPHYS ACTA
SELDEN S C	1983	258	7064	J BIOL CHEM
STEINER B	1990	9	3539	EMBO J
VERA J C	1988	85	6763	P NATL ACAD SCI USA
WISCHIK C	1988	100	1905	J CELL BIOL
WISCHIK C M	1985	100	1905	J CELL BIOL

L89 ANSWER 27 OF 27 USPATFULL on STN
 ACCESSION NUMBER: 2003:258371 USPATFULL
 TITLE: Compositions with vascular damaging activity
 INVENTOR(S): Davis, Peter David, Aston Rowant, UNITED KINGDOM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003181424	A1	20030925
APPLICATION INFO.:	US 2003-367606	A1	20030214 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2001-GB3668, filed on 15 Aug 2001, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2000-19944	20000815
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LADAS & PARRY, 26 WEST 61ST STREET, NEW YORK, NY, 10023	
NUMBER OF CLAIMS:	14	
EXEMPLARY CLAIM:	1	
LINE COUNT:	471	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions for the inhibition of the formation of new vaculature by angiogenesis are provided as in compounds which are salts comprising as an acidic component a compound of formula (1) wherein: R.sup.1, R.sup.2 and R.sup.3 are each independently alkyl, R.sup.4 is alkoxy, haloalkoxy, alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl, hydroxy or halo, R.sup.5 is hydrogen, alkoxy, alkyl,

alkylthio, hydroxy, phosphate or halo, and, as the basic component, a compound selected from the group consisting of (2) a compound of formula (2) wherein R.sup.6 is hydrogen or alkyl R.sup.7 is alkyl, alkylamino, dialkylamino, nitroamino, hydrazine, mercapto or alkylthio X is CH.sub.2, CH.sub.2CH.sub.2, CH.sub.2S, CH.sub.2CH.sub.2S Y is NH or S or a compound of formula (3) wherein R.sup.8 is alkyl or aminoalkyl R.sup.9 is hydrogen, alkyl or optionally substituted phenyl or, a compound of formula (4) wherein Z is O, S, CH2, CHR13 or a bond R.sup.10, R.sup.11, R.sup.12 and R.sup.13 are each independently alkyl or hydrogen or, a compound of formula (5) wherein R.sup.14 is alkyl and the pharmaceutically acceptable solvates and hydrates thereof.

IT 222030-63-9

(prepn. and use of cis-stilbene derivs. with vascular damaging activity
)

IT 2149-70-4

(prepn. and use of cis-stilbene derivs. with vascular damaging activity
)

FILE 'HOME' ENTERED AT 15:47:17 ON 13 JUL 2004